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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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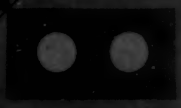

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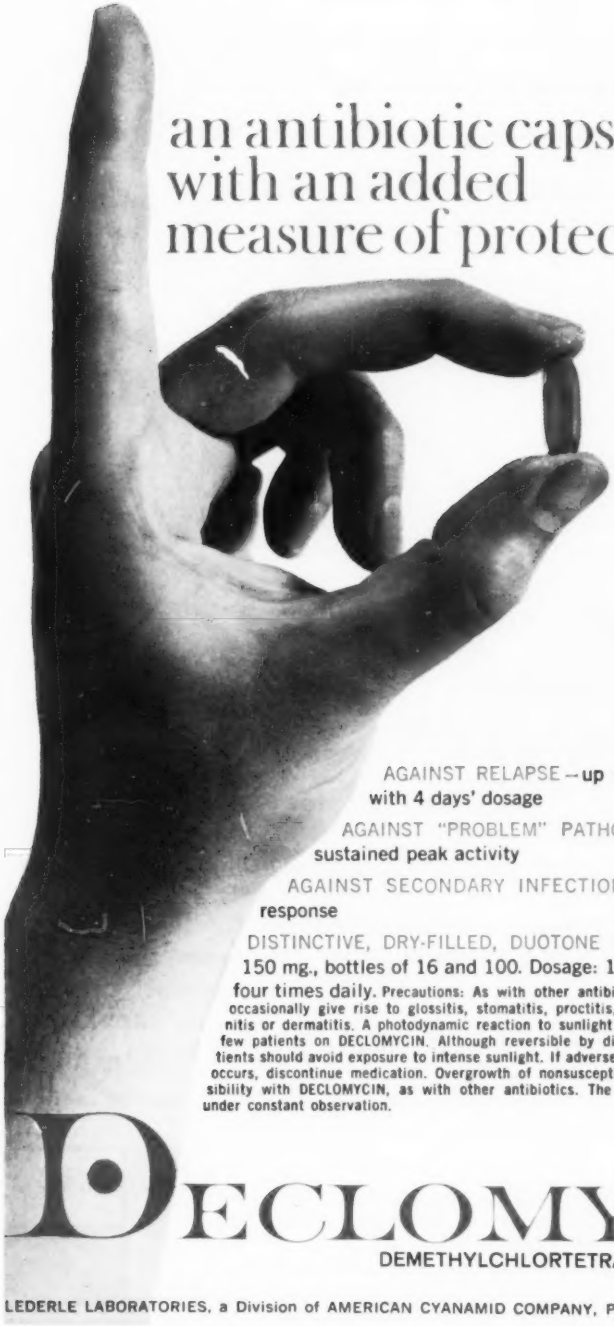

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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THE DEVELOPMENT OF THE FEDERAL ROLE IN THE SUPPORT OF MEDICAL RESEARCH*

JAMES A. SHANNON

Director, National Institutes of Health, Bethesda, Maryland

THE growth in Federal funds for medical research and in the policies and decisions under which they are expended constitutes a most significant influence upon national medical research activities, medical education, and to a large degree the financial status of medical schools and universities. Questions which this development has thrust before us have become prime issues of national policy. The manner in which these questions are answered will have far-reaching consequences, not only for medical research but also for medicine as a whole.

I should like to trace briefly the origins of this Federal responsibility and the development of programs for the support of research through grants. My reading and observations on the historical backgrounds are, of course, those of an amateur. It is my intention to sketch some of the important events and the context in which they arose, in the interest of better understanding and more reflection upon the important problems before us.

* Presented at the meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, November 18, 1959.

The Present Support of Medical Research

Until modern times medical research was supported by the Federal Government almost solely in response to specific problems associated with national emergencies. Current Federal programs go far beyond this. Efforts to replenish the store of basic knowledge are broadly recognized as essential to the success of research in problem areas. As a result, there has been a transition from the earlier pattern of supporting ideas and projects to the support of men of known productivity and achievement. Thus, the full flowering of programs based upon this broad view requires, on the part of the supporting agency, a full and mature sense of responsibility for both the requirements of the public interest and the needs of science and scientists.

What is the current level of medical research support, and what in general are the sources? It is estimated that in 1959 the total national expenditure for medical research from all sources, public and private, will total $575 million. A little over half (51 per cent) of this amount will come from the Federal Government. The remainder will come from a variety of nonfederal sources, including industry, the foundations, voluntary agencies, and other private and public organizations. In contrast, national medical research expenditures in 1940 totaled only $45 million, and the Federal share was less than 10 per cent.

As this demonstrates, the explosive growth of Federal medical research expenditures is largely a postwar phenomenon. However, the pattern of relationships among private and public institutions in which current programs operate has prewar precedents and origins, some of which emerged in the last century. These events, in turn, were a consequence of forces and influences that shaped fundamentally our development as a people and a Nation.

Early Federal Attention to Medical Research

Only in a full-scale history could one hope to delineate and assess adequately all the influences that have shaped the role of the National Government in medical research. An outstanding work in this respect is *American Medical Research* by Dr. Richard H. Shryock. This evocative and perceptive inquiry into the interplay of economic, social, political and scientific forces in relation to medical research was published in 1947 under the sponsorship of this Academy's Committee on Medicine and the Changing Order.

Federal interest in science and scientific activities is by no means new. There has been an almost constant interplay between government and scientific activities from the beginning of our Federal Republic. A. Hunter Dupree, in his superb study *Science in the Federal Government*, makes the point clear:

> "From the beginning the Federal Government has rendered honor to science and profited from it. . . . Through all the twists and turns of the political history of the United States and through the immense changes wrought by 150 years of rapidly expanding scientific knowledge, the policies and activities of the Federal Government in science make a single strand which connects the Constitutional Convention with the National Science Foundation."

You will remember that this nation was born in the "Age of Reason". Our Constitution was designed and our early development guided by men whose philosophical views reflected the political and scientific ferment of the 18th century. The names of Franklin, Jefferson, Rush and Rittenhouse are indicative of the kinds of interests and viewpoints that attended early government-science relationships. Much of this interest was directed toward the pressures of our frontier, internal improvements, and the basic agrarian economy of the day. These concerns dominated the development of national scientific relationships for the better part of the 19th century.

During the first half of that century, medicine and the beginnings of medical science were chiefly matters for individual activity and private support. There was little that could be called medical research. The medicine of the day was dominated by theoretical concepts that explained all disease in terms of single pathological systems and discouraged systematic inquiry and observation.

The impetus for change came primarily from Europe. Thus American medicine in the past century reflects the British influence at the beginning, the French viewpoints in the pre-Civil War period, and German developments during the latter half.

The United States Public Health Service

In this early background, one event of significance to the later role of the Federal Government in medical research appears. In 1798 the Fifth Congress passed an act to provide for the care of sick and disabled

merchant seamen. This law, providing for the establishment of a series of Marine Hospitals, constitutes the legal beginnings of the United States Public Health Service. It was not until late in the century, however, that the organization created by this legislation, then known as the Marine Hospital Service, appeared in any meaningful role in the national medical research scene.

The Geological Survey and the U.S. Department of Agriculture

During the latter part of the 19th century, the relationships of science in government emerged first in connection with problems of land management and natural resources and, secondly, in the growth of agricultural science and the development of the Department of Agriculture. Both of these series of events have had real meaning for the later development of Federal medical research.

John Wesley Powell, geologist, explorer, prophet of the dust storm, and bureaucrat of the 1880's, developed a philosophy of government relationships to science in fighting through the role and functions of the Geological Survey. The establishment of this professional and scientific organization provided basic precedents for a clear Federal role in scientific activities. The biological research activities instituted by the Department of Agriculture and the evolvement of the Agricultural Research Program, with its State and land-grant college relationships, contributed to the substance of medical sciences through research. It also provided a pattern of organization and Federal-State cooperation which has greatly influenced other Federal operations.

The State Boards of Health and the American Public Health Association

It is in the post-Civil War scene that the beginnings of a broad national health and medical research role for the Federal Government appear. This was a period of great interest in public health in the states and among physicians and public officials. The first modern State Board of Health was set up in Massachusetts in 1869. The American Public Health Association was organized in 1872.

The National Board of Health

In 1879 a bill passed the Congress, creating a National Board of Health. I wish to dwell on the establishment of this Board for a moment because the activities it undertook constitute the first organized, com-

prehensive, national medical research efforts of the Federal Government.

The Board was set up to deal with a practical public health problem. In 1878 a severe yellow fever epidemic had revealed the inadequacy of existing means for dealing with communicable diseases of this nature. The board was comprised of seven members appointed by the President. It included representatives of the Army, Navy, Marine Hospital Service and the Justice Department. Significantly, one of its functions was to "Obtain information on all matters of public health". The original bill also provided authority—deleted before enactment—for grants-in-aid to State Boards of Health.

The record of this Board is remarkable. Among the able men appointed to it was John Shaw Billings, an Army Medical Officer. Billings was a distinguished intellectual and administrator—a rare combination. He had conducted a study resulting in the reorganization of the Marine Hospital Service in 1870 and was to figure prominently in the national medical scene for the remainder of the century. Billings became Vice-Chairman of this National Board and its dominant and guiding member.

The Board initiated a research program, largely under the design and direction of Billings, which included the following activities:

1. Dispatch of a yellow fever investigation commission to Cuba.
2. Revision of a standard nomenclature of disease.
3. Development of a vital statistics program in cooperation with the Tenth Census of 1880.
4. Conduct of field sanitary surveys.

Finally, the Board provided financial aid to scientists in universities through grants for the conduct of research on problems of interest to the Board. This, I believe, was the first use of the Federal grants-in-aid device for the support of research in nonfederal institutions. It was the beginning of the project grant system.

The Board, unfortunately, was short-lived. Its support of research, involving the expenditure of $30,000 in all, was considered extravagant by the Congress. In administering national quarantine functions, the Board incurred the opposition of state agencies, private shipping, and interestingly enough, the Marine Hospital Service. In 1882 its appropriations were transferred to the Marine Hospital Service, which carried on the Board's quarantine functions, but did not continue its general program of public health research or the research grant program.

It was not until 1912 that the broad public health and medical research function exercised by the National Board was finally authorized for the Federal Government. The concept of Federal grants-in-aid for support of medical research in universities and research institutions, though revived briefly during World War I in connection with control of venereal diseases, was not incorporated into law until the National Cancer Act of 1937.

This sequence of events indicates clearly how the evolution of Federal activities is in fact limited by fundamental factors outside the control of bureaucrats. Not the general concepts of the role of the Federal Government, the state of science itself, nor the structure and scientific capacities of universities were developed in the 1880's to the point where a strong Federal effort in support of the medical sciences was comprehensible or feasible.

The United States Army

Following the National Board, the center of Federal medical research shifted to the Army. A small and gifted group of men under the influence of Billings and the leadership of Sternberg began a period of research given impetus by the exciting developments in bacteriology emanating from Europe and the work of Pasteur and Koch. The intensive work of Army scientists on yellow fever had its origins at this time, culminating in the dramatic achievements of Reed and Gorgas.

Philanthropy and the Universities

In the latter part of the 19th century, the Federal role in the medical sciences was viewed as limited to the problems involved in the control of epidemic disease. The greatest promise for medical research lay in private support and the use of the universities. Three major circumstances significant for medical research emerge at this time:

First were the developments in the medical and related sciences and the attendant resurgence of interest in science and research brought about by the discoveries of Pasteur, the theories of Darwin, the growing sciences of bacteriology, physiology and pharmacology, and the new concepts of the specificity of disease identification and cause.

Second was the importation of the concept of graduate study in the sciences, following the German model. This was initiated at Johns Hopkins and spread rapidly in succeeding decades.

Third was the accumulation of great private fortunes that were to be made available for the support of science and education under the influence of Andrew Carnegie's "Gospel of Wealth"—the philanthropic return of profits to society as the obligation of the wealthy.

Thus began the great period of private support of higher education and the sciences, soon to be effected through establishment of philanthropic foundations.

The transformation of private giving from help-the-needy to imaginative, constructive philanthropy aimed at strengthening the fundamentals of our society was the feat of a few foundations and farsighted individuals. The Flexner Report revolutionized medical education. And the Rockefeller Foundation pioneered in new forms of support for science—first the underpinning of whole institutions and later the support of projects. These developments have had tremendous and generally unrecognized effects upon the later development of Federal activities.

Federal Research in Public Health Programs

A small event in this epoch which marks a beginning must be noted. In 1887 a young Marine Hospital Service Officer, J. J. Kinyoun, returned from Europe inspired by what he had seen in the German research laboratories. In that year he set up a small bacteriology laboratory in the Marine Hospital on Staten Island. This laboratory, later designated as the Hygienic Laboratory, was moved to Washington, where it grew slowly, concentrating on problems of infectious diseases.

In the first decade of the 20th century, there was a second period of intense national concern with public health problems and the need for a stronger Federal role. These developments were a part of the beginning reactions to the economic dominance of the large private concentrations of wealth. There was an increasing tendency to view the Federal Government as a means of exercising social control. The Progressive movement led by Teddy Roosevelt, the struggles over pure food and drug legislation, and the conservation of natural resources were reflections of this new viewpoint.

Federal health functions were substantially modified in the process. In 1902 an act was passed changing the name of the Marine Hospital Service to the Public Health and Marine Hospital Service. Shortly thereafter, a biologic control function was added. In 1906 the Food & Drug Act was passed. Further efforts were under way for the creation of a

comprehensive national health agency, and several bills for this purpose were introduced into the Congress. President Taft urged the establishment of such an agency in two successive State of the Union messages. These broad proposals were defeated by a vigorous combination of anti-vivisectionists, Christian Scientists and medical sects. In compromise, the Act of August 14, 1912 was passed, slightly broadening Federal health responsibilities.

This act for the first time stated in law the responsibility of the Public Health Service to " . . . study and investigate the diseases of man and conditions influencing the propagation thereof . . ."

Grants to Scientists in Universities

Not until World War I was the device of supporting medical research through grants-in-aid to university scientists resumed. The Chamberlain-Kahn Act of 1918 for the study and control of venereal diseases authorized an annual appropriation of $285,000 for each of three years to be used for research. These studies were carried out by the Interdepartmental Social Hygiene Board and the Public Health Service's Division of Venereal Disease, both created by the Act. The Board made grants to some twenty-five institutions for studies related to venereal disease. More importantly, it clearly established the precedent for the Federal Government to seek the assistance of the research scientists of the nation through the form of Federal grants-in-aid in matters determined by Congress to be in the public interest.

The National Institutes of Health

In 1930 Congress passed an act reorganizing and expanding the functions of the Hygienic Laboratory, changing its name to the National Institute of Health.* This law also authorized for the first time the establishment of research fellowships. The Service's research function, however, remained strictly intramural.

The 1930's

An interesting and almost-forgotten phase of the development of the Federal Government's role in the support of science and research was the depression activities of the WPA (Works Progress Administration). Under its Federal Research Projects Program, Federal funds were

* Changed to National *Institutes* of Health in 1948.

given to aid scientific and research activities in State universities, public institutions, and agencies. It is interesting to read today the names of the investigators whose work was supported by Federal funds in those lean years. Among them are many of the outstanding scientists of the country today.

The New Deal brought about profound changes in the concept of the role of the Federal Government. Among these was the idea that the Government had a responsibility to act in major problems affecting the national health. In this context the National Cancer Act was passed in 1937. It established the National Cancer Institute and for the first time provided permanent authority for making grants in support of medical research in nonfederal organizations.

The research support program of the Cancer Institute in pre-World War II days was modest. Between 1938 and 1940 it awarded 33 grants in the amount of $220,000.

World War II and the Postwar Period

World War II demonstrated to the nation the immediate and potential significance of science and technology in our national destiny —as epitomized in the successful development of the Atomic Bomb. Large amounts of Federal money were spent on research to solve war-born problems. A major influence in this program was the Office of Scientific Research and Development under the direction of Dr. Vannevar Bush.

In response to President Roosevelt's inquiry concerning the measures which the Federal Government should take to make research useful to the public and to aid research in nonfederal institutions in the postwar period, Dr. Bush prepared his now famous report, "Science, The Endless Frontier." The fundamental, and then-controversial, idea of this report was that the required impetus for research in the nation could come only from the Federal Government. He recommended the establishment of a National Research Foundation, with a research program to be carried out by grants or contracts with private institutions. Proposed for this agency was a maximum budget of $122,500,000 after five years, of which $20 million would be for the medical sciences. Many thought this level of expenditure visionary.

Dr. Bush's recommendation, modified in many ways, was finally enacted in 1950 as the National Science Foundation Act. This au-

thorized the National Science Foundation, which was established the following year, with responsibility for support of basic research.

During this immediate postwar period, several major changes occurred in the Federal structure for research in the life sciences:

The Public Health Service Act of 1944, reorganizing and recasting the Public Health Service statutes, provided broad authority for the conduct and support of all kinds of medical research. At the end of the war the remaining research-support program of the Office of Scientific Research and Development in the field of medical science was turned over to the National Institutes of Health to administer under this authority.

Legislation providing for new national institutes was enacted in rapid succession—the Mental Health Act in 1946, the Heart Act and the Dental Research Act in 1948. Other institutes now comprising the National Institutes of Health were established under authority of the Omnibus Research Act of 1950.

The Office of Naval Research undertook a broad program of support of university research in biology and medicine.

The Armed Forces Epidemiological Board extended its work.

A re-invigorated Veterans' Administration established firm and productive links between many of its hospitals and medical schools. This served as the basis for a strong medical research program.

The Atomic Energy Commission took responsibility for a broad spectrum of investigations relating to the effects of radiation upon biological systems.

As Dr. Charles V. Kidd of the National Institutes of Health pointed out in his recent book, *American Universities and Federal Research*, "The significance of the rapid and smooth assimilation of scientific activities, particularly those having to do with the support and purpose of research, by the operating parts of the Executive Branch and immediately after World War II, can hardly be overemphasized as a factor affecting Federal science policy."

Reasons for the Postwar Expansion in Research Support

What gave rise to this sudden broadening of Federal medical research activities? Popular recognition of the significance of science and research for the welfare of the nation was primarily responsible. The war had revealed the enormous economic capability of the nation and

the heights to which man's efforts can reach, particularly when aided by science and technology. A conviction that a significant portion of the resources of the nation could be productively directed toward the conquest of disease and for the well-being of man underlies these events. At the same time, economic developments were such that—for better or worse—neither private fortunes nor the resources of state and local governments were adequate to finance a large-scale medical research effort. And industrial spending had been applied largely to inquiries designed to increase profits rather than strengthen science generally.

Finally, the medical and biological sciences themselves matured rapidly in the war and postwar years. For the first time in the history of science, these fields of inquiry became ripe for intensive exploitation. The process of maturation has continued at an exponential rate, and the needs for financial support have risen more than proportionately.

We have, in short, been in an unprecedented situation in which public expectations have been translated into political pressures for action, at a time when extended support was indicated on scientific grounds. This happened in an era when the required funds could not be produced by private activity alone. These forces underlay the postwar development of the Federal role in medical research.

As a consequence, we have witnessed continued increases in the appropriation of funds by the Congress. Funds available to the National Institutes of Health for research grants alone rose from $3.5 million in 1947 to $97 million in 1957—nearly a 30-fold increase. During fiscal year 1960, NIH will expend almost $200 million in the form of grants for research projects.

The Present National Structure for Research Support

This sudden acceleration in research support has presented NIH and, in a very real sense, the nation, with a new series of complex problems involving the fundamental relationships of the Federal Government, science, and the universities.

The first clear delineation of these issues was set forth by consultants to the Secretary of Health, Education and Welfare in the well-known Bayne-Jones Report* of two years ago. This group of distinguished

* The Advancement of Medical Research and Education through the Department of Health, Education and Welfare: Final Report of the Secretary's Consultants on Medical Research and Education. Government Printing Office, Washington, D.C., 1958. (Available from Office of Research Information, National Institutes of Health, Bethesda 14, Md.)

men concluded in summary that the nation could look forward to further increases in the magnitude of its medical research activities. They emphasized, however, that the prospect demanded further action in respect to the training of medical and research manpower and to the financial stability and independence of universities and medical schools. It may be noted that the national expansion of medical research as predicted in this report has already been exceeded. In this respect the Bayne-Jones Report has erred in the same way as many previous reports—notably, those of Bush, Steelman and Reed—that represented in their time bold visions of the years ahead. Consistently, the development of medical research and the Federal role have been grossly underestimated.

The major problems that loom before us center in three basic issues:

1. Finding means to contribute to the basic stability of institutions of higher learning in a manner that enhances their freedom and strengthens all their functions.
2. Providing mechanisms that will permit the development and support of stable careers for research investigators within the tenure systems of the universities.
3. Devising a way to work effectively with universities, medical schools, and research institutes as a whole in the development of policies and programs.

Our proposals for the payment of the full costs of research and for a system of Institutional Research Grants, drawn from the recommendations of the Bayne-Jones Research Committee, are directed to these ends. Developments in the current scene emphasize the importance of building broad support programs with total institutional needs clearly in view. The Public Health Service proposal for an institutional research program constitutes our first step in this direction, and may represent the beginning of a whole new trend in Federal support of science.

In the solution of the problems before us, we shall need the advice and guidance of all who have thoughtful concern not only with the means but also the purposes and ends of a national medical research effort.

ALPHA-CHYMOTRYPSIN IN CATARACT SURGERY*

The James W. Smith Memorial Lecture

MR. LEONARD H. LAKE, M.B., B.S., D.O.M.S.

Consultant Surgeon, The Royal Victoria Infirmary, Newcastle-upon-Tyne, England; Clinical Teacher in Ophthalmology, School of Medicine, University of Durham

Few would deny the superiority of the intracapsular technique of cataract extraction over its predecessor, the extracapsular technique, but fewer still would deny the risks, both operative and postoperative, inherent in the intracapsular technique and its limitation to patients of the older age groups, because of the toughness of the zonule in the younger subjects. It has always been a matter of some difficulty to decide at what age one could, with reasonable safety, embark upon the intracapsular technique. The difficulties and complications that can be encountered in an extracapsular extraction are well known to us all. These, together with the possibility of postoperative complications, particularly iritis, have to be equated with the possibility of even more serious difficulties which can be encountered in an unsuccessful intracapsular extraction, where, perhaps after the rupture of a somewhat resistant zonule, the capsule strips, the vitreous face ruptures, and one is left with the unenviable task of removing as much of the lens matter as possible, whilst attempting to leave behind the vitreous, only to have, as a final result, an updrawn pupil, a secondary glaucoma, or, as a late result, a retinal detachment, as the fruits of one's labours.

I am sure we have all been faced with this dismal sequence of events. The operation of zonulotomy is difficult and hazardous, and it is obvious that these difficulties were at the back of the mind of Barraquer, when he was searching for something which would dissolve the zonule and so render easier, and comparatively safe, the removal of all save the infantile cataracts by the intracapsular method. It was fortuitous, therefore, that in 1957, whilst injecting a 1 in 500 solution of alpha-

* Presented at the Meeting of the Section on Ophthalmology, The New York Academy of Medicine, February 15, 1960.

chymotrypsin into the vitreous for a stubborn vitreous haemorrhage, he noticed that, days later, the lens was dislocated. This suggested to him that alpha-chymotrypsin was the substance for which he had been searching for some years. He thereupon carried out experiments, mostly on rabbits and hares, then later on human eyes, firstly enucleated and finally *in vivo*, with various strengths of alpha-chymotrypsin, to determine the strength which would produce the necessary zonulysis in a reasonable length of time, without producing intra-ocular side effects.

The early experiments which he carried out did prove that:

1. The action of alpha-chymotrypsin was effective in a concentration of 1 in 5000, without producing any other noticeable intra-ocular side effects.

2. This solution, injected into the anterior chamber, produced dislocation of the lens in some 25 minutes, and thereafter the cataracts could be extracted with an erysiphake, using a vacuum of something less than 40 cm. of mercury.

3. There were no postoperative complications attributable to the use of this drug, and he came to the following conclusions:

[*Literal translation of Barraquer's preliminary report of April, 1598.*[1]]

"That the use of this enzyme opened the way to phakoresis of the crystalline lens at any age, thus displacing the extra-capsular extraction, and therefore eliminating such complications as capsular retractions, secondary cataracts, and irido-capsular synechiæ on the one hand, and on the other, in intra-capsular extraction, the difficult technique of zonulotomy, capsule tearing, the detachment of the retina by excessive traction in order to tear the zonule, inflammatory reactions of the ciliary body by mechanical forces, and loss of Vitreous due to pressure traction manoeuvres in order to attain the zonular ruptures. Furthermore total extraction of the crystalline lens in high Myopia can be obtained in all ages, the classic Sperina, Fukala Vacher operation with all its inconveniences being eliminated. The presumed dangers of retinal detachment will diminish on suppression of the tractions necessary to break the zonule mechanically."

It was at this stage, July, 1958, that I was fortunate enough to be offered supplies of alpha-chymotrypsin (Chymo-Trypure Novo), which at that time were not readily available, for experimental work, in order to assess the validity of the claim made by Barraquer[1, 2] and also to attempt to evaluate the type of case in which this drug would be of particular use. I decided, therefore, that I would carry out a series of 100 cases of cataract extraction, using the drug according to Barraquer's

technique, and that the drug should be used in all cases irrespective of any particular indication; and furthermore, that only those cases operated on at one hospital, namely, the Royal Victoria Infirmary, Newcastle-upon-Tyne, using the same staff, technique and instruments, etc., should be included in the analysis, so that the results of the operations would be strictly comparable with 100 cases operated on without the use of the enzyme.

Little attempt at selection of cases was made, and the only criterion for *not* using this drug in the cases included in the experimental series was that the lens should be seen to be dislocated, either before or immediately after the corneal section had been made. The first series of 200 cases, i.e., 100 cases using chymotrypsin, and 100 cases without the use of the drug, was completed last September (1959), and a second series is now being carried out; but it is on the results of the first series that this paper is based.

The analysis has included the preoperative, operative and postoperative findings, both early and late, and complications in both series.

At the beginning of the experiment it became obvious that an efficient vacuum pump erysiphake was an essential part of the armamentarium, and such an instrument not being in our possession to start with, the early extractions were carried out by capsule forceps, with or without expression. Some difficulty, however, was experienced in removing certain lenses. There were several situations where, after zonulysis, either the capsule proved too tense to grasp due to intumescence of the lens, or else the lens capsule was degenerate and ruptured the moment the forceps were applied; or the vitreous was threatening to prolapse, making expression difficult. Because of these difficulties, it was considered that an erysiphake was absolutely necessary. Fifty-eight per cent of the lenses in the series were removed with this instrument, the remaining 42 per cent of the cases being dealt with by forceps and expression.

The technique of the operation, in so far as the use of the alpha-chymotrypsin is concerned, is essentially that described by Barraquer in his preliminary report.[1]

Following corneal section and peripheral iridectomy, a 1:5000 solution of alpha-chymotrypsin is injected into the posterior chamber by means of a lacrimal cannula, and allowed to remain until zonulysis has occurred, the average time being about two and one half minutes per patient. When zonulysis has taken place, it will be noticed that the lens

has come forward and bulges the iris in front of it, and a little gentle counterpressure below will show that the lens is in fact floating free of the anterior vitreous face. At this stage the anterior chamber should be irrigated with Ringer's solution prior to the removal of the lens.

At the time of commencement of this experiment, I was using a method of corneal section with a preformed conjunctival flap, and preplaced corneal scleral sutures through preformed corneal scleral grooves, which I did not think was a method universally practiced, and believed to be rather peculiar to myself. I have, however, learned recently that this technique is also used in this country, and has been reported in the *American Journal of Ophthalmology*. I should say that I have been using this technique for the past eight years, and I saw no reason to alter it for the purpose of this investigation.

The technique is, however, purely coincidental, and any technique preferred by the individual surgeon can, of course, be used. I note that Barraquer himself used postplaced corneal scleral sutures following the corneal incision. Furthermore, he irrigated the lower posterior chamber through the pupil, and the upper posterior chamber through the peripheral iridectomy. This latter manoeuvre, I think, is rather dangerous, as there is a danger that the solution may be injected into the vitreous, and I feel that for this reason vitreous losses have occurred where they would not normally have done so. Therefore, I now irrigate only through the pupil, both above and below. There seems to be some variation in the potency of the various preparations of chymotrypsin which are on the market. The particular brand which I have been using seems to give the best results in a concentration of 1 in 5000.

I have furthermore proved to my satisfaction that the drug, in the concentration in which we use it, appears to be without any marked deleterious effect upon the rest of the intra-ocular structures. It is, however, my practice to wash out any excess of zonulysin after the lens has been removed, by irrigating the anterior chamber, although this practice is not, I believe, followed by all surgeons.

When zonulysis is complete the lens can be removed in one of three ways*:

1. It can be withdrawn with capsule forceps, by grasping the upper part of the lens, and drawing it forward through the pupil, provided that: (a) the pupil is dilated sufficiently; (b) the capsule is thought to

* All three methods were demonstrated by a motion picture film shown before the conclusion of the lecture.

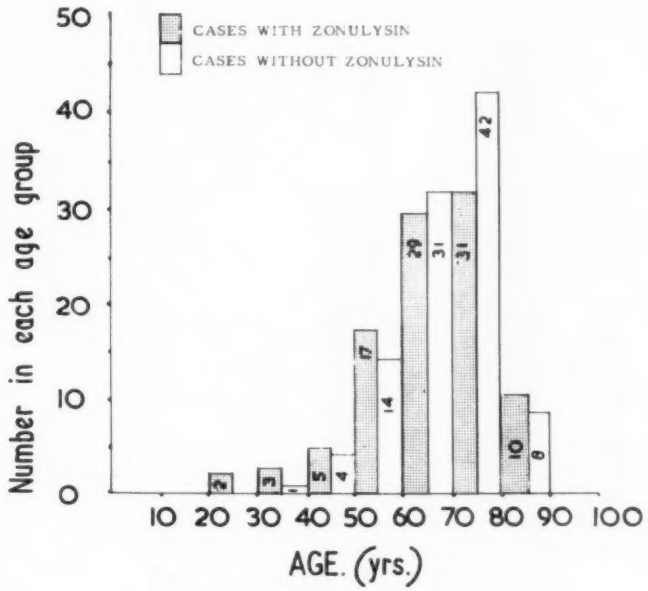

Fig. 1. Age distribution of patients.

be healthy enough to withstand the traction necessary to withdraw it; (c) the lens is not intumescent, and the capsule can be picked up.

2. It can be milked out, as in the old extracapsular extraction, with an expressor, either with or without a vectus to assist it.

3. It can be removed with the erysiphake.

As I have said before, my own preference is for the last method, as it seems to give the most consistent result; but, as will be seen on the film later, some cases invite withdrawal with capsule forceps, and some merely invite expression with a lens expressor. The only contraindication to erysiphake extractions is that I have noted that the incidence of striate keratitis with this type of removal is higher than in the other two. I feel this difficulty is due to instrumentation, and I am hoping that, by the use of a smaller and better designed instrument, we may get less of this complication. The instrument which I am using at the moment is rather on the large side.

I would like to present the result of this comparative study of the two series of cases.

Age distribution of cases (Figure 1): It can be seen from the graphs

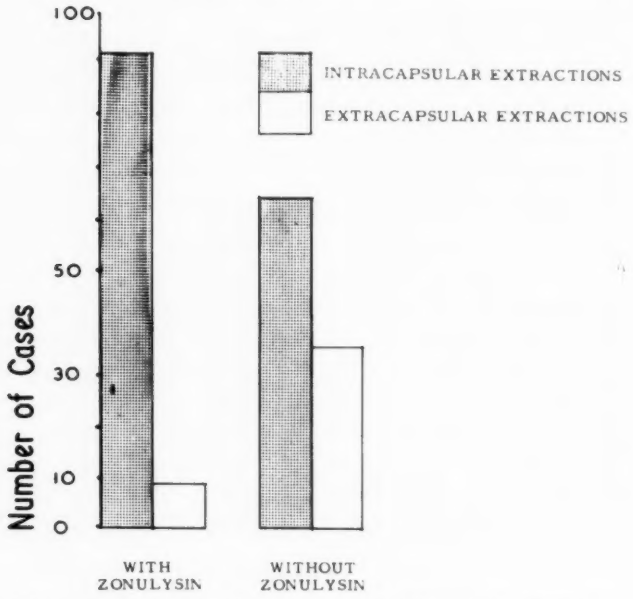

Fig. 2. Comparison of intracapsular with extracapsular extractions.

that the age distribution in the experimental series is wider than that in the control series. This is not purely coincidental, and it will be seen that two cases occurred in the 20-30 group, 3 in the 30-40 group, and 5 in the 40-50 age group. Correlating this with the high incidence in intracapsular extractions, it will be seen that it is possible to obtain an intracapsular extraction at a much earlier age with chymotrypsin.

Incidence of successful intracapsular extractions (Figure 2): If it is agreed that the hall mark of successful cataract extraction is that a successful intracapsular extraction should be carried out, it will be seen that the first and most important finding is the incidence of intracapsular extractions in each series. The results are, to say the least, quite striking.

It can be seen that, without the use of chymotrypsin, 65 per cent of cataract extractions were intracapsular, and the remaining 35 per cent were extracapsular. This compares with 92 per cent in the series using chymotrypsin, only 8 per cent being extracapsular extractions. In the control series the 35 extracapsular extractions have been analysed, and this analysis shows that 29 are classified as failed intracapsulars, i.e., an intracapsular extraction had been tried and failed, the usual cause being

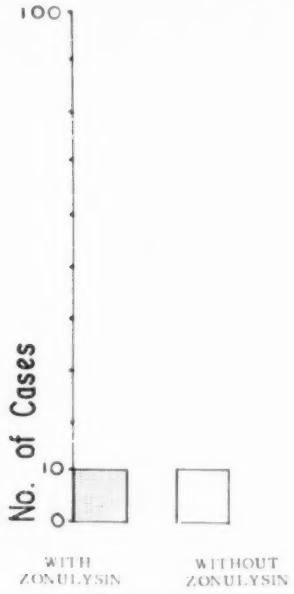

Fig. 3. Vitreous loss.

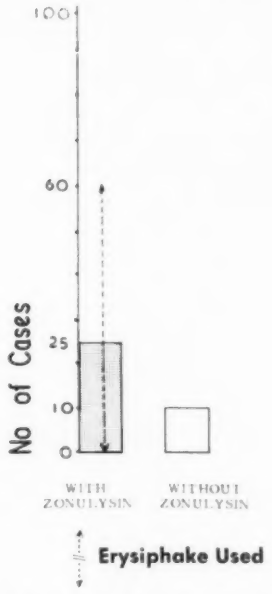

Fig. 4. Incidence of striate keratitis.

the stripping of the capsule before the tearing of the zonule. Amongst these 29 cases, four were diabetic, two were hypermature cataracts, one was morganian, three were cases of exfoliation of the lens capsule, six were cases of old iridocyclitis, one was traumatic, and two were glaucoma cases. Amongst these cases five had vitreous losses, four of which occurred in myopic eyes. With regard to the eight extracapsular extractions carried out in the experimental series, four occurred early in the series before the erysiphake was available, and four were carried out with the erysiphake. Amongst these, two were diabetics, two were complicated cataracts, and one was a traumatic cataract. Amongst these cases, two sustained vitreous losses. Complete zonulysis was obtained in 89 per cent of the cases, seven cases produced incomplete zonulysis and four could be classified as only poor. These cases of incomplete zonulysis occurred fairly early in the series, whilst we were still experimenting with the concentration of the solution, which at that time was obviously too weak.

Vitreous losses (Figure 3): These amount to 11 per cent in each of the series. In the control series, seven occurred with intracapsular extrac-

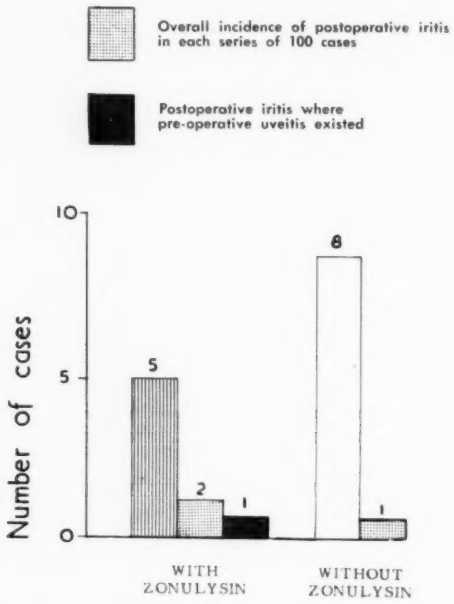

Fig. 5. Incidence of pre- and postoperative uveitis.

tions and four with extracapsular, including one diabetic and one glaucoma patient, who had had a previous filtering operation. In the experimental series (in which chymotrypsin was used), nine occurred with intracapsular extractions, and two occurred in those cases where only extracapsular extractions were possible. Of these, one was a traumatic cataract, and one had vitreous in the anterior chamber before extraction. Amongst the nine, four were myopic.

In the experimental series where loss of vitreous occurred, it was noticed that the vitreous was fluid, and it is suspected that the enzyme does have a liquifying effect on the vitreous. Further studies on the effect of the enzyme on vitreous are indicated. Where vitreous loss occurred, air was injected into the anterior chamber at the end of the operation, after the sutures had been tied, and there were subsequently no postoperative complications as a result of this loss. To date, no secondary glaucoma or updrawn pupils have been recorded.

Striate keratitis (Figure 4): Here it will be noted that there is a distinct increase in the number of postoperative striate keratitis. In the

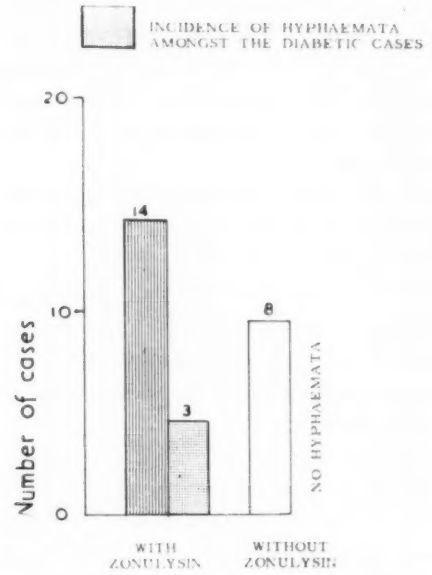

Fig. 6. Incidence of diabetics in each of 100 cases and incidence of hyphaemata in relation to diabetic cases.

control series, 10 per cent of cases showed this condition; but in the experimental series, 25 cases were recorded. Of these, seven were severe, one lasted for six months, and one for three weeks; but all eventually cleared. In most of these cases, the erysiphake was used to extract the lens, and I feel that the keratitis must have been due to the pressure of the instrument on the back of the cornea, and not due entirely to the chymotrypsin. The possibility that the enzyme has a softening effect on the endothelium cannot be excluded. In the control series, of course, the erysiphake was not used at all, as this instrument is more or less useless in the absence of a degree of zonulysis.

Iritis (Figure 5): *Incidence where preoperative iritis existed:* In the experimental series, five cases showed signs of preoperative iritis or iridocyclitis, and in the control series, eight showed the presence of previous similar inflammation. In the experimental series, four intracapsular extractions were carried out. In the control series only two were intracapsular. No postoperative iritis occurred in any of the cases in the control series, and only one in the experimental series.

Incidence of primary postoperative iritis: Postoperative iritis occurred in the control series in one case only, and in two cases where chymotrypsin was used. In the latter series one was a specific iritis and the other a non-specific. Both responded to corticosteroid therapy locally—one was severe and might be attributed to the use of the enzyme in too strong a concentration.

Diabetes (Figure 6): There were eight diabetics in the control series, all of whom had diabetic retinopathy, and four of whom had successful intracapsular extractions, i.e., 50 per cent.

In the experimental series there were 14 diabetics, four of whom subsequently were found to have retinopathy, and in 11 of these diabetics, the cataracts were removed intracapsularly, i.e., 85 per cent. There was no postoperative iritis, or material increase in the incidence of hyphaema, in these diabetics.

Occurrence of hyphaemata in each 100 cases (Figure 7): There were 15 hyphaemata in the control series, five of which were operative. There were no diabetics amongst these. In the experimental series there were 14 hyphaemata, all of which were small, only 1-2 mm., 8 of which were operative. There were three diabetics in this series. The hyphaemata in both series absorbed spontaneously, and none had to be evacuated in either series. An increase in the incidence of hyphaemata, which might indicate some delay in wound healing, has not occurred.

Preoperative glaucoma: In the control series there were five cases, and in the experimental series four cases, where preoperative filtering operations had been carried out. The over-all number of glaucomas in the control series was eight, three of which were secondary, as a result of exfoliation of the lens capsule; and in the experimental series, five had glaucoma, one of whom had not had a previous filtration operation. No significant change in the glaucomatous state which could be attributed to alpha-chymotrypsin occurred.

Postoperative capsulotomy: In the control series, one required two needlings and one required three needlings. None of the cases in the experimental series has yet required a needling of the after-cataract.

Myopia (Figure 8): There were eight cases of myopia in the control series, and 14 in the experimental series. Of those in the control series, four were removed intracapsularly, i.e., a total of 50 per cent, and of these, two subsequently developed retinal detachment, and one developed iritis. That was the only case of iritis in the control series.

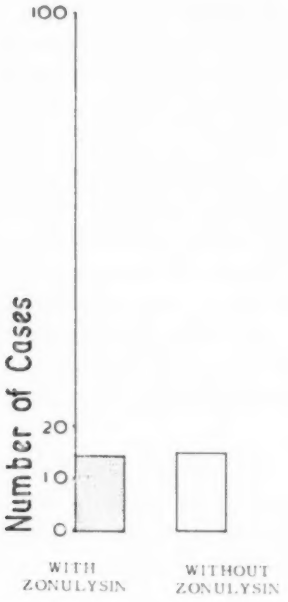

Fig. 7. Incidence of hyphaema.

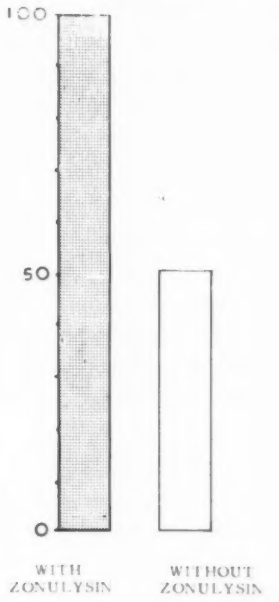

Fig. 8. Incidence of intracapsular extractions in myopia.

In the experimental series there were 14 cases of myopia and 14 intracapsular extractions, i.e., 100 per cent. There were four cases of vitreous loss amongst these, and one case of iritis, the old specific iritis which I mentioned before. No cases of retinal detachment have occurred in the experimental series to date.

Conclusion: From the results presented, I think it can be claimed that a high percentage of intracapsular extractions can be expected when this drug is used. Furthermore, these extractions appear to be free from many of the disadvantages of the old intracapsular technique, where the zonule had to be ruptured mechanically, and the lens tumbled out, with all the risks enumerated by Barraquer. I consider that alpha-chymotrypsin is a valuable adjunct to successful cataract surgery, particularly in younger patients, where it would not normally be possible to obtain an intracapsular extraction, or where the incidence of postoperative retinal detachment is commonly substantial.

The selection of cases for use of the drug must remain a matter of choice for the individual surgeon. Many feel that it should be reserved

for the young patient, where the zonule is known by experience to be tough, and that the drug is unnecessary in the older age groups. On the other hand, in juvenile and infantile cataracts the use of chymotrypsin would appear to be contraindicated on account of the hyaloido-capsular adhesions present up to the age of twenty years. It should be recognized, however, that not all such cases are bound to lose vitreous, which can sometimes be stripped off the posterior capsule with an iris repositor under direct vision when the lens is drawn gently forward with either capsule forceps or erysiphake. In a few cases, moreover, it may even seem preferable to lose a little vitreous than to risk a severe phako-anaphylactic endophthalmitis in a second eye, when needling and linear extraction have given poor results in the first eye, and repeated needlings have failed to produce a skiable gap in the tough and fibrous posterior capsule.

Although not included in this series, the youngest case that I have operated on for a cataract, a child four years of age, had had unsuccessful needlings in one eye for congenital lamellar cataract. At operation, an intracapsular extraction was possible after only three minutes of zonulysin.

Finally, it does seem that this drug is relatively innocuous in the concentration in which I have used it, always providing that the excess is washed out. Many criticisms have been made with regard to the use of chymotrypsin, but I think that most of these can be regarded as not due to the drug but perhaps to impurities or faulty technique. For my own part, I feel I shall continue to use it in almost every case as a routine. I hope that, at a later date, I shall be able to publish the results of the second series.

ACKNOWLEDGMENTS

I would like to acknowledge the help given to me in the operations, and in the preparation of these statistics, by Mssrs. Harold F. Lake, Martin C. Kemp, and Ian Menson. Also, I am indebted to Mr. Ridley and Miss Watts for their preparation of the film, and to Mssrs. Evans Medical Specialities, Speke, Liverpool, who placed the supplies of Chymo-Trypure Novo at my disposal for use in experiments. I must say that the preparation which they have supplied me has been of a high standard, and very consistent results have been obtained with it.

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CURRENT THERAPY OF PULMONARY TUBERCULOSIS

*Transcription of a Panel Meeting on Therapeutics**

JOHN H. McCLEMENT . . . Moderator

Assoc. Professor of Medicine, College of Physicians and Surgeons, Columbia University; Visiting Physician-in-Charge, Chest Service, Bellevue Hospital, New York

Panel Members

AARON D. CHAVES

Asst. Clinical Professor of Surgery, College of Physicians and Surgeons, & Preventive Medicine, Cornell University Medical College; Supervisor of Clinics, Bureau of Tuberculosis, Department of Health, New York

AARON HIMMELSTEIN**

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* Presented at the *Monthly Panel Meeting on Therapeutics (7th Series)* of The New York Academy of Medicine.

** Deceased, December 18, 1959.

MODERATOR MC CLEMENT: This afternoon's panel is composed of both physicians and a surgeon, representatives from two hospitals in New York especially concerned with the treatment of tuberculosis, and a representative of the New York City Department of Health, an organization that plays a very important role particularly in the outpatient treatment of tuberculosis in our community.

As you all know, the last ten or twelve years have seen tremendous advances in the treatment of tuberculosis. This has come about principally because new and very potent chemotherapeutic agents which are effective against the tubercle bacillus have been made available to us. Improvement has also resulted from major advances in the field of thoracic surgery during this same period, as evidenced principally by the increased use of resectional procedures in the thorax. These improved results have been shown not only in more rapid control of the disease process but in the more certain control of tuberculosis, and, in some instances, the control of tuberculosis where it never could have been controlled in earlier periods.

This afternoon we propose to discuss this subject, and to present to you what we believe to be the principles that currently apply in the treatment of this disease. I believe this problem should be discussed in two or three categories, and to keep order in our discussion I should like, if possible, to restrict our discussion to these various categories.

The initial diagnostic studies that must be carried out in each patient before a case of tuberculosis can be treated rationally, must be considered in terms of the clinical, bacteriologic, radiologic findings that are essential to characterize the disease process to be treated. Secondly, we must consider the problem of initial treatment in caring for those patients who come to us with tuberculosis who have never been treated before; and thirdly, how to deal with retreatment cases, which usually represent treatment failures in which we try a second time to retrieve the case where there has been initial failure. In following this discussion pattern, I should like to try to identify and illustrate, or have the panelists identify and illustrate, the general principles that are applicable in the treatment of this disease. I have brought some case material which, at an appropriate time, I shall show and ask the panelists for their opinion as to how these particular cases should be managed. I shall leave time at the end of the session for questions from the audience.

Before considering the first case I shall ask the members of the panel for comment on two of the questions I have raised. Let us deal first with studies deemed essential to characterize the patient, in establishing the diagnosis of tuberculosis before treatment is undertaken.

I shall begin by asking Dr. Chaves what he considers to be an orderly diagnostic approach to a patient in whom the diagnosis of pulmonary tuberculosis is suspected.

DR. AARON D. CHAVES: I would like a combination of at least two of the following: Either a roentgenogram of the chest which shows pulmonary disease compatible with tuberculosis, together with either bacteriologic confirmation of the presence of tubercle bacilli—and I don't want to go into details as to how that can be done; as you know there are many organisms that may simulate the tubercle bacillus and these should be excluded—and/or the presence of a positive tuberculin test. I believe that the combination of a positive tuberculin test with certain roentgenographic findings, even in the absence of positive sputum, may be sufficient indication to start treatment.

MODERATOR MC CLEMENT: *Would you agree with this, Dr. Riley?*

DR. EDGAR A. RILEY: I agree with Dr. Chaves. I think it is appropriate to mention that a detailed medical and social history, and a careful physical examination should precede the laboratory studies outlined by Dr. Chaves.

MODERATOR MC CLEMENT: Yes, I certainly agree with that, and I think Dr. Chaves was trying to identify those things he considered essential.

Are there some essential findings not mentioned by Dr. Chaves that you think should be present before you embark on the treatment of a patient with suspected tuberculosis?

DR. RILEY: If one suspects the roentgenographic picture is that of tuberculosis in which the activity of the lesion may be undetermined, it is important to assemble all previously taken x-rays of the patient in order to compare them with the present film and determine if there has been any roentgenographic change. It is, as I am sure you all know, quite difficult to determine from a single roentgenogram whether the lesion is clinically active or inactive.

MODERATOR MC CLEMENT: When you are satisfied that you are dealing with a case of active tuberculosis in a patient subjected to the techniques you mention, what studies do you consider essential, not neces-

sarily to confirm the diagnosis, but to characterize the disease in order to help you plan a course of therapy? For instance, *do you think that most patients who are being treated for the first time should be tested to determine the susceptibility of their tubercle bacilli to the commonly used antimicrobials?*

DR. RILEY: Dr. Chaves has done some interesting work on that, and perhaps he can cite exact figures. Actually, in the initial treatment cases, the incidence of primary bacterial resistance to any one of the three major drugs is so low that as a routine procedure the determination of drug susceptibility is unnecessary.

DR. CHAVES: If I may speak briefly on that subject, I should like to point out that most clinics do not believe that primary resistance of the organisms to the three major anti-tuberculosis drugs, streptomycin, para-aminosalicylic acid (PAS) and isoniazid is an important clinical problem; therefore, patients are assumed to be harboring organisms which are susceptible to all three, with some rare exceptions. But even in centers where drug resistance in untreated patients is considered to be a problem, treatment need not be withheld while the results of such tests are awaited. This could delay treatment for a period of four to six weeks, or even longer. In England a favored routine is to start patients with suspected active tuberculosis on treatment which includes all three major drugs until the results of the drug susceptibility tests have been returned from the laboratory. Then, should the organisms be found susceptible, two drugs of choice are continued, whatever they may be, usually isoniazid with one of the other two drugs. However, should there be evidence of even partial resistance to one of the major drugs, this is taken into consideration in continuing the chemotherapeutic program.

MODERATOR MC CLEMENT: Dr. Himmelstein, later in the patient's course you may be called on to carry out surgical treatment. Looking ahead to that time, *are there diagnostic studies that you think should be carried out in this initial evaluation period that will make your understanding and surgical management of the patient easier?*

DR. AARON HIMMELSTEIN: I feel more strongly about the evaluation of the organism for drug resistance, because the complications of surgery occur in those patients whose organisms are resistant to drugs. I would like to know whether initially the organisms were sensitive to the drug, and then, as the period of treatment develops, one can retest

the latest organisms recovered, to see whether drug resistance has developed. I think that the avoidance of complications of surgery in the present era depends largely on the organisms being sensitive to drugs. I, for one, advocate an early evaluation. Frequently we lose the organism. We may have an organism disappear from the sputum, only to reappear later and then find it to be drug resistant. I would like to know where we stood initially with this drug. Aside from this, there does not appear to be much else of importance, from the surgical aspect, in the early treatment of the lesion.

MODERATOR MC CLEMENT: We shall take up the indications for surgery in our subsequent discussion, but just to anticipate for a moment, let us consider the indication presented by a persistent open cavity. *Do you think such cavitary lesions can be more easily identified at this late period in the patient's course if they have been well documented from the very beginning, or do you advocate the use of body section radiography in most patients early in their course?*

DR. HIMMELSTEIN: Yes, relatively early in their course. I think in most ordinary cases where cavities are rather clearly identified and the lesion restricted in nature, it is not hard to locate the lesion on each film, but frequently that is not true. I think body section technique does help to show us where the cavities were originally, and may tell us whether the lesions that are seen late in the course of the disease are the same lesions which were present earlier. For this reason I believe in the value of and advocate early taking of body sections.

MODERATOR MC CLEMENT: This also is not just restricting ourselves to body section radiography but a careful evaluation of the lesion by x-ray. The use of oblique and lateral films also helps in making a precise identification of the location, which may be of use in any subsequent surgical management.

DR. HIMMELSTEIN: Yes, I think that is useful. That technique is used which best demonstrates the lesion. This may be accomplished by a good PA film and lateral films, if the lesion is rather limited in extent. If it is well visualized on these two views, oblique or so-called lordotic views may also help to define the lesion rather clearly. The patient is not exposed to body section radiography as a routine procedure. However, this technique may prove helpful later in the course of the disease in locating the site and extent of the original lesion and indicating the present size of the cavity. Cavity walls frequently become very thin

and difficult to see.

MODERATOR MC CLEMENT: I think we should now move on to the second group of questions which I should like to pose to the panel before presenting a specific case. Because of the systematic and carefully controlled work done by the Veterans Administration in this country and by the Medical Research Council in England, we do have some facts that suggest that certain chemotherapeutic regimens are superior to others. We recognize that this material comes to us from a great mass of observations on individual patients, that it has some of the pitfalls associated with such material, and that there may be areas where exceptions can be taken from the conclusions that are drawn from it. *From this material, Dr. Riley, and from your own experience, what do you consider the best drug regimen for the initial treatment of patients with susceptible organisms?*

DR. RILEY: I think there is little question that, in the initial treatment of a case, any drug regimen should include isoniazid, which is by far the most potent, the least expensive, and the least toxic of all our antituberculosis drugs. This drug can be used either alone or, more generally, in combination with either PAS or with daily or intermittent streptomycin. There have been no statistical studies either from the Veterans' Administration, the Public Health Service, or from abroad which clearly puts one combination significantly ahead of the other in its effectiveness. At Bellevue Hospital, for example, most cases of moderately advanced cavitary tuberculosis do very well on a combination of isoniazid and PAS. It is my feeling that minimal lung lesions or tuberculosis of the lymph nodes and perhaps acute tuberculous pleurisies with effusion do quite well on isoniazid without PAS. PAS, as you probably know, is a rather unsatisfactory drug in some respects. It has many gastrointestinal side effects, toxicity is not uncommon, and the average dose varies between 24 to 30 tablets a day. It is an unpleasant drug to take over a period of one, two, or even three years. I think the results of the V. A. work have shown that a combination of triple drug therapy using PAS, streptomycin and isoniazid, produces no better long-term results than the combination of PAS and isoniazid alone. Triple drug therapy probably should be reserved for patients who are acutely ill with acute miliary tuberculosis, with tuberculous meningitis, or perhaps with far advanced acute caseating tuberculous pneumonia. There is a certain value in withholding streptomycin from

the average new case, as the drug may be needed later on to cover either an operative procedure or some sort of emergency not foreseen at the onset of treatment.

MODERATOR MC CLEMENT: *Any additions to these remarks, Dr. Chaves?*

DR. CHAVES: I should like to caution against one particular regimen in patients who are excreting tubercle bacilli, and that is isoniazid combined with twice weekly injections of streptomycin. I think this is a bad combination for the disease that might go on to complications or to residual cavitation with continuing positive sputum, because dosage of streptomycin twice a week has not been shown to be substantially effective in delaying emergence of resistance to isoniazid. The use of isoniazid in combination with streptomycin twice weekly is not sufficiently better than isoniazid alone, to warrant the risk of development of streptomycin-resistant organisms. Therefore if, when treatment is started, the combination to be used is isoniazid with streptomycin until such time as the sputum becomes negative for tubercle bacilli, I would strongly urge that streptomycin be used daily. Whether this regimen is continued for three months or six is a matter of opinion, but certainly it is desirable to continue until such time as the patient becomes sputum-negative.

MODERATOR MC CLEMENT: *Have you any comments on this medical problem, Dr. Himmelstein?*

DR. HIMMELSTEIN: Certainly, from the surgeon's point of view, we always like to have a potent agent in reserve at the time we operate, one that has not yet been used in treatment, and in this eventuality I would prefer to have streptomycin available. From personal knowledge of the V.A. hospital results I would agree that any regimen that begins the treatment of tuberculosis should include INH. My own choice would be INH and PAS, withholding streptomycin for a possible subsequent major emergency, or for later surgery.

MODERATOR MC CLEMENT: *Will you continue and tell us what patients in this initial treatment group do require surgery and how to identify such patients?*

DR. HIMMELSTEIN: Very briefly, surgery can accomplish removal of the residua of treatment of tuberculosis when drug treatment has been in effective use for a period of time. The field for surgery is becoming more and more limited. Early in the era of drug therapy the

results of surgery were very good. The mortality and morbidity of resection by lobectomy and/or segmental resection for tuberculosis were quite low, approximately one per cent or less. At the beginning of the period of drug treatment and of resectional surgery it was generally held that any residua of any significant size, and particularly cavities, should be resected. However, with additional information concerning the good results of long-term drug treatment of tuberculosis, and the fact that the small residua of tuberculosis left in the lung after good medical management did not cause any serious difficulties, the field for surgery in this particular area became restricted. At the moment, I think that we should resect all cavitary lesions of tuberculosis, and, just to introduce some controversy, let me suggest that all open cavities should be resected, positive or negative, whether or not organisms can be recovered in the secretions. I believe we should resect the large lesions of tuberculosis, those visible by x-ray after treatment and a centimeter or a centimeter and a half or more in size, particularly those lesions which develop and can be identified as filled-in cavities and which have caseous material in them. These lesions may erupt at a later date into the tracheo-bronchial tree. When the lesion can be identified as one which has been present throughout the period of treatment, which has never been an obvious cavity, and which now measures a centimeter or less in size, then medical treatment, if carried out faithfully, is perhaps preferable to surgery, since it does not expose the individual to the hazards of operation, and the morbidity and mortality associated with surgery. That, briefly, is our point of view at the moment. Obviously this applies only to pulmonary tuberculosis, and not to the treatment of lymph node or pleural tuberculosis.

MODERATOR MC CLEMENT: In laying down these criteria for the selection of patients for surgery, *would you admit that there are some patients with cavities and solid lesions who should be operated on but who, because of the extent of their disease or other complicating disease, cannot be operated on?*

DR. HIMMELSTEIN: I have tried to indicate those patients who should be considered for surgery. The patients not to be considered for surgery form an equally large group, and this is true particularly of those with bilateral tuberculosis, in whom the problems are somewhat different from those I have outlined.

MODERATOR MC CLEMENT: *Dr. Chaves, are you in disagreement with*

any part of Dr. Himmelstein's last statement?

DR. CHAVES: I should like to comment on all of his statement, if I may, and the best way for me to do that is to give my own ideas of the indications for surgery in tuberculosis today. To my mind, the primary indication is a patient who is still excreting tubercle bacilli following a reasonably adequate period of chemotherapy.

What is reasonably adequate depends on what is shown on the x-ray, the clinical picture and many other things. I would say that after a minimal period of six months, and certainly after six to twelve months of treatment, a decision regarding surgery should be made in a patient with localized tuberculosis still excreting tubercle bacilli,—that is, a cavity.

MODERATOR MC CLEMENT: *The only criterion that you would use is bacteriologic? You are not concerned with whether there is an obvious open cavity or not?*

DR. CHAVES: That, to my mind, is the most important criterion. Beyond that there are other borderline areas, and I would consider the patient with a residual localized cavity, whose sputum is bacteriologically negative, as a case for surgery, but that again would depend on how old or how young the person was, how rapidly the sputum converted, and whether the cavity had a thin bleb-like wall or was a thick-walled cavity. Rather than becoming too involved, and taking too much time, I would say these are borderline areas for resection.

When confronted with the solid lesion, I personally would refuse to commit myself to a surgical procedure based on a ruler, that is to say, up to so many centimeters we would advise operation, and larger than that we would not. I know of no statistical evidence which indicates that, under sound, prolonged chemotherapy, the breakdown rates of the solid foci, no matter how large or how small, are any different among those lesions resected and those medically treated and adequately supervised. We have pathological evidence that if the foci are removed they do contain caseous material and, in some instances, organisms. That, for me, does not indicate proof that reactivation would have occurred in the future.

MODERATOR MC CLEMENT: Let me now present a patient with very limited disease, and ask for comment on the treatment of such a patient.

(Slide) This is the x-ray of a young man in his twenties. The lesion, a very small lesion seen in the right apex, was discovered as a result of

examination at the patient's place of employment in 1952. An x-ray taken a year previously was completely normal. The patient was asymptomatic, afebrile, had no physical findings, his tuberculin was positive, his sputum was negative on smear. I think those are the essential data. I can provide you with additional data if you like. *Using some of the general principles that we have talked about, Dr. Riley, how would you handle such a patient?*

DR. RILEY: I think, although this is a situation in which cavities are not easily demonstrable on the routine film, tomograms might very well show a cavity. This would influence my choice of therapy because I think a non-cavity lesion like this might do very well on isoniazid alone, but were a cavity present I should prefer to have the patient on a combination of isoniazid and PAS. This patient should probably have at least two years of uninterrupted drug treatment. A minimal lesion of smaller extent than this should be treated for at least a year, but possibly even longer, depending upon the extent of residual disease failing to show resolution.

MODERATOR MC CLEMENT: This body section radiograph was taken. There was no apparent cavity. However, other and better films did show that there were satellite lesions adjacent to this, and therefore it was presumed that bronchogenic spread had occurred in the development of this lesion, but *you would treat him either with isoniazid alone or with isoniazid and* PAS, *and your decision between these two would be based on whether there was or was not a cavity present?*

DR. RILEY: I think I might be more inclined to combine PAS if the sputum were positive on culture, since a positive culture can only come from disease with cavitation.

MODERATOR MC CLEMENT: This you wouldn't know for another six or eight weeks.

DR. RILEY: I would start with isoniazid and PAS, but might consider stopping PAS if, after six or eight weeks, his cultures were negative and no cavity were demonstrated.

MODERATOR MC CLEMENT: *Dr. Chaves, what is your view of this?*

DR. CHAVES: With that lesion complex, I would not hesitate to start the patient on an INH-PAS regimen. Just one word of warning. We have not mentioned differential diagnosis and we have talked glibly about starting patients on anti-tuberculosis therapy, even without bacteriological confirmation. I have become very allergic to any kind

of pulmonary lesion which is confined within one lobe, let alone one segment. Even in a younger person with a positive tuberculin test, and even with the telltale satellite lesions on x-ray, which certainly would speak more for tuberculosis or fungus disease than for neoplasm, I think one should keep other possibilities in the back of one's mind while treating such a patient. Neoplasm would be foremost, but even a transient pneumonia should be thought of, as well as a number of other pulmonary diseases—such as Loeffler's syndrome, residuals of previous inflammatory disease, mycotic infections or the many other lesions that might occur and resemble this. I cannot help becoming involved in the subject of diagnosis.

MODERATOR MC CLEMENT: This is indeed a very important subject. Do you have any other comments, Dr. Himmelstein, on this patient at this point and particularly on Dr. Chaves' last point that in treating tuberculosis we must be aware that we are fallible?

DR. HIMMELSTEIN: I think one must be aware of that and pursue other diagnoses, but this is so likely to be tuberculosis that I would do a number of gastric tests on him and then probably start INH and PAS treatment. During the period of investigation I would do skin tests for various fungi and pursue other diagnoses, but this is still undoubtedly tuberculosis.

MODERATOR MC CLEMENT: Actually, the patient was managed much in the fashion that you suggest. Tubercle bacilli were subsequently found in material obtained for culture during this initial period of evaluation.

(Slide) This slide shows the clearing which occurred in the next nine months or so and we are left here with a solid round encapsulated caseous focus, I suspect with some areas of fibrosis which are illustrated even better on the tomographic section (Slide), here a solid lesion, there some suggestion of little satellite lesions about it. The sputum converted promptly early in his course of chemotherapy, and we now have him at the eight or nine month point. *How would you manage him now, Dr. Chaves?*

DR. CHAVES: I would agree with Dr. Riley that today we would probably treat such a case for a period of two years. I don't believe it makes too much difference at this point whether he continues on the isoniazid combination with PAS, or on isoniazid alone. I have no scientific or statistical reason for backing up my feeling that once the

point of x-ray stability and sputum conversion is reached, it is quite adequate to continue on just isoniazid alone. I would be inclined to treat him with isoniazid and PAS for one year and continue with isoniazid alone for another year.

MODERATOR MC CLEMENT: *Do you agree, Dr. Riley?*

DR. RILEY: That sounds like a sensible approach.

MODERATOR MC CLEMENT: *Neither of you two medical men would think of surgery in a patient such as this at this time?*

DR. RILEY: No, but I suspect that back in 1952 he might very well have had a resection.

MODERATOR MC CLEMENT: But we shall deal with him as though treating him today.

DR. CHAVES: I might go even further and say that by this time he would be back at work, had I managed him!

MODERATOR MC CLEMENT: *You would not disagree?*

DR. RILEY: It would depend on what kind of work he did. If he had a sedentary occupation, I might not have stopped him from working at all. If he were a ditch digger or did heavy manual labor, I don't think I would have him go back to work after eight months.

MODERATOR MC CLEMENT: *Dr. Himmelstein, would you operate on this man?*

DR. HIMMELSTEIN: No, not now. I would like to ask Dr. Chaves why, if he has a patient who takes PAS successfully for a year, he stops it if it does not bother the patient who has been able to take it for a year?

DR. CHAVES: I don't know that I would stop it in a patient who took it for a year without difficulty.

DR. HIMMELSTEIN: You said you would just stop at the end of the year and let him take INH alone.

DR. CHAVES: I was thinking of the average patient with a good deal of difficulty in taking PAS. Most patients will take it in spite of gastrointestinal complaints, although they may have to vary the dosage at times. But if the patient is greatly upset, I don't think it is worthwhile to persist in giving the medication after the first year. However, if I have a patient who can take PAS with no discomfort, I would continue the regimen unchanged for the two years.

MODERATOR MC CLEMENT: (Slide) He had a segmental pulmonary resection, and I think this illustrates how one of our views has changed

since 1952, when the treatment of such lesions was weighted more in favor of surgery than it is today. This photomicrogram shows solid encapsulated caseous foci scattered about, and there are some areas of scarring and fibrosis. Although his sputum had been negative throughout the latter part of his course, tubercle bacilli were grown from this specimen, and he was treated with streptomycin-PAS, as was the custom at that time. There were resistant organisms present, so I suspect he may have been somewhat better off for having the resection done but, as Dr. Chaves has said, certainly many patients like this are now being treated without surgery, and with excellent results.

There is one large group of patients which I think we shall have to consider in a rather cursory fashion because our time is getting short, and that is the group of patients in whom treatment has failed, and we are obliged to treat those patients who have resistant organisms. The next patient whom I would like to present to the panel illustrates such a case.

(Slide) This patient was a 34 year old Negro woman who had had tuberculosis intermittently since adolescence. This film was made in 1955, and by that time she had had more than three years of intermittent treatment with streptomycin, PAS and isoniazid. She was admitted to the hospital at the time this x-ray was taken because she had had an hemoptysis. Her sputum was easily positive. The organisms isolated from it were resistant to these three major therapeutic agents. On physical examination, in addition to signs of the tuberculosis which were seen on x-ray, there was evidence of diffuse bronchitis; breath sounds at the bases were somewhat emphysematous in character, and there was evidence of bronchospasm, which was relieved by bronchodilators. She said that she had shortness of breath on rather slight exertion. She remained in the hospital at the time this x-ray was taken for only three weeks and then, as is so often the case with patients who have had prolonged chronic disease, she became impatient with her progress and left the hospital, to return at the time of the next film.

(Slide) This shows the course of the disease during the next year. She now had a huge cavitary lesion in the left upper lobe with a fluid level in it, and as I have said, her tubercle bacilli were completely resistant to drugs, and the physical findings described at the time of her first admission were still present. *How would you treat this type of patient, Dr. Chaves?*

DR. CHAVES: This kind of patient should best be treated by attempting to prevent the condition shown at this stage. Proper treatment of the patient in the first place would include not only medical therapy but proper timing of surgery. I don't know how cooperative this patient was.

MODERATOR MC CLEMENT: On this second admission there were times when she was cooperative; at the time of the admission now under discussion, she was in a more cooperative mood than on the first admission.

DR. CHAVES: But am I right in assuming that she was not too cooperative in the early phases of the disease?

MODERATOR MC CLEMENT: That is true.

DR. CHAVES: This is not the result of improper medical management of the patient, but rather the failure of the patient to permit the medical team to do everything that should have been done for her in the first place.

MODERATOR MC CLEMENT: That is true. Her early history was characterized by repeated short interrupted admissions with chemotherapy.

DR. CHAVES: I can only emphasize the obvious importance of proper medical and surgical management at the time the patient is first seen, in order to prevent situations such as this. We are faced with this kind of problem all too frequently. Because of her extensive disease and poor pulmonary function, I am afraid in this case the only approach is medical, even though she already shows evidence of drug resistance *in vitro*. What degree of drug resistance was demonstrated?

MODERATOR MC CLEMENT: Complete.

DR. CHAVES: To isoniazid, streptomycin and PAS, I assume. I would then put her on isoniazid in combination with one of the other as yet unexploited drugs. Any reason for using isoniazid in combination with some other drug is this: I do not believe that the *in vitro* susceptibility to isoniazid *necessarily* reflects the situation in this person's lung with regard to isoniazid drug susceptibility. It holds true for streptomycin, but there is not quite a similarly close correlation between laboratory and clinical resistance to isoniazid. Therefore, I would put her on isoniazid and combine this with one of the other second-line drugs, such as cycloserine, or kanamycin or viomycin. I would prefer not to use pyrazinamide in this kind of case, unless as a last resort, because of its hepato-toxicity. Pyrazinamide is a good drug to cover surgery in re-

sistant cases, because it is a drug that is best used over a relatively short period of time; but for this chronic type of case one should have a drug that can be used for a year or a year and a half. This would be risky with PZA but might be worth while in selected cases.

MODERATOR MC CLEMENT: Dr. Himmelstein!

DR. HIMMELSTEIN: This is one of the worst things that can happen in tuberculosis, repeated short periods of treatment with a drug which does not control the disease but renders the organisms insensitive to the drug. When faced with a problem like this, it is necessary to use a drug regimen which will bring the patient to surgery in the best possible condition. Dr. Chaves has indicated some of the drugs which are available. That is the approach to this situation but, as he has said, this is treatment failure.

MODERATOR MC CLEMENT: Dr. Riley!

DR. RILEY: I would agree with what Dr. Chaves has said regarding his choice of drugs. I think that this is perhaps one situation where we should go back to fortifying our drugs with the old concept of complete bed rest. It seems to me that this woman obviously had no host resistance against her disease and did badly. Perhaps by adding bed rest to the drug regimen she might, at some future date, be brought into shape for a surgical procedure by Dr. Himmelstein.

MODERATOR MC CLEMENT: *Do you think, Dr. Himmelstein, there is any place for collapse therapy, or is this a surgical technique that is only of historical interest?*

DR. HIMMELSTEIN: There is still occasional use for collapse therapy, particularly in bilateral tuberculosis. I would not say it is only of historical interest because, before all of the present techniques were available, we were curing or, if not curing, certainly controlling tuberculosis effectively with thoracoplasty in a large majority of patients operated upon. This is a technique which, when all other methods have failed, or may not be used, should still be thought of and used effectively. Bilateral disease is usually one situation in which collapse therapy is used with greatest effect; however, by and large, excisional surgery is now the preferred procedure.

MODERATOR MC CLEMENT: It was considered for this patient because of her respiratory insufficiency. However, it was thought that the hazard of opening her left chest, and carrying out a fairly extensive resection, carried with it an expected prohibitive morbidity and mortal-

ity, so she was treated somewhat in the fashion suggested by Dr. Chaves. Treatment with isoniazid was continued, and viomycin and pyrazinamide were added to her regimen. It was recognized that pyrazinamide, as Dr. Chaves said, has a very short period of effectiveness, and accordingly this regimen was followed for a short period of time only. In a few weeks her sputum was reduced dramatically in volume, and tubercle bacilli disappeared from it. During this period, an upper stage thoracoplasty was carried out and collapse of this cavitary lesion was obtained. Her sputum became negative at that time and remained negative from then until her death later that year. On her return before her terminal illness, there were signs of respiratory insufficiency which had bothered her throughout her later course, and she died of respiratory insufficiency, with evidence of *cor pulmonale*. Whether the thoracoplasty contributed to this or whether this was just the expected evolution of her disease, tuberculosis complicated by bronchitis and emphysema, I don't think we can say.

DR. HIMMELSTEIN: Thoracoplasties are still occasionally done in preparation for lobectomy. It controls the amount of sputum in some instances and is still a very useful procedure, but is used much less often than formerly.

DR. CHAVES: What was done for this patient, in terms of pulmonary function tests, before surgery?

MODERATOR MC CLEMENT: Pulmonary function tests were done, and they demonstrated that she had evidence of bronchitis and emphysema, with a reduced maximal breathing capacity. The operation produced no great change in these conditions.

There are many questions we could pursue on this general subject, but I made two promises to the panel and the audience: I promised Dr. Riley that he could leave at five o'clock because he has to catch a train, and I promised the audience that they would have an opportunity to ask some questions. In the remaining time, admitting that we have not covered this complex subject completely, I think we should deal with some of the questions submitted by the audience. One of these questions should be of particular interest to Dr. Chaves because of his association with the Department of Health of New York City. He is greatly concerned with the out-patient or out-of-the-hospital management of patients with tuberculosis, and the question is: *Can a patient with moderately advanced pulmonary tuberculosis be safely treated at*

home by a general practitioner; and if so, what regimen should be instituted? This will give you a chance, Dr. Chaves, to give us your ideas on the place of the hospital, the clinic and the private office, in our program for patients with tuberculosis.

DR. CHAVES: I could best sum up my answer to this type of question by saying that, in general, for a patient with uncomplicated, moderately advanced pulmonary tuberculosis, assuming the sputum is positive, assuming there is no problem in diagnosis, and assuming that the patient is not a difficult medical or nursing problem, the indications for hospitalization for such a patient are mainly social; that if the home situation is good, and the patient can afford to have a private physician who understands how to manage the patient, or will call on some expert to assist him in this management, there is no reason why that patient should not do as well at home as in the hospital. If necessary, even tomography can be done on an out-patient basis. Surgical consultation can be had, good bacteriological studies can be carried out, and a drug regimen of isoniazid and PAS, an easy one to carry out at home, is the one I recommend, to avoid a regimen involving injections. I think one should be on the alert for drug toxicity in the early phase of treatment, particularly with PAS. Beyond that, I think there is no particular problem.

QUESTION: How is this disease spread?

DR. CHAVES: I stipulated that home conditions should be satisfactory, which I thought covered the problem of isolation. Tuberculosis, once diagnosed, is not a very contagious disease, if the patient is intelligent and cooperative under proper treatment, and in a home in which he can be isolated or separated from the rest of the family. That does not have to be a walled-up room. I think there is now evidence to show that such patients cared for in the home do not infect other uninfected members of the household.

MODERATOR MC CLEMENT: Our group at Bellevue Hospital has been trying to study this particular aspect of tuberculosis management, and our preliminary conclusion is that patients under treatment and under observation do not constitute an appreciable risk of contagion to their family or the community. This is particularly so if all of the characteristics of the patient and the home that Dr. Chaves has mentioned are present.

Dr. Riley, I have a question about the treatment of pleural effusions. *Do the general principles that have been mentioned here for the treat-*

ment of pulmonary tuberculosis apply equally well to the treatment of pleural tuberculosis?

DR. RILEY: Yes, I believe so. There is no question but that the incidence of the later development of parenchymal tuberculosis is markedly reduced if, at the onset of the acute pleurisy, drug therapy, preferably isoniazid with or without PAS, is begun, and maintained for at least 12 months and possibly for as long as 18 or 24 months.

MODERATOR MC CLEMENT: *Dr. Chaves, do you concur in this?*

DR. CHAVES: I do.

MODERATOR MC CLEMENT: Dr. Himmelstein, in addition to being a very fine surgeon, is also a physiologist of some repute, so this question is appropriately addressed to him: *Do you think there is any reason why a patient with arrested tuberculosis should not fly in jet planes which may fly at altitudes of 30,000 or 40,000 feet, pressurized, of course, to 8,000 feet?*

DR. HIMMELSTEIN: No. The only reason for a patient not to fly is that he is unable to tolerate a simulated altitude of 3,000 to 5,000 feet. If his pulmonary reserve is such that exposing him to a 3,000 to 5,000 foot altitude may be a problem, he should not fly. However, there are few patients who would be in a position to fly under these circumstances, since they would be too ill to be traveling by plane, and this would present a rather rare problem. It will not affect his tuberculosis, certainly, and functionally there is no problem. The pulmonary reserve in minimal or moderately advanced tuberculosis is such that this is no real difficulty.

DOCTOR: Would you please read the question as I stated it? There were some other points.

MODERATOR MC CLEMENT: Would you prohibit a patient with arrested tuberculosis, who is subject to hemoptysis, from making trips on such planes, when planes are pressurized down to 8,000 feet?

DR. HIMMELSTEIN: "Subject to hemoptysis" covers a lot of ills. I think such patients have active tuberculosis. I would like to know how much tuberculosis they have, since the jet plane that flies at a cabin pressure equivalent to 8,000 feet does put a slightly increased burden on the patient. If it is not necessary for him to fly in a jet plane, I would suggest that he fly in a propellor-driven plane.

DOCTOR: Or take a train!

MODERATOR MC CLEMENT: Actually, I know that many of the air

lines believe that, with very few exceptions, if a patient is able to travel at all, he can travel by air.

I have two additional questions for Dr. Chaves. One is, *has glycosuria been observed with treatment with isoniazid*, PAS, *or streptomycin?* I am sure it has been observed in diabetics who are receiving these drugs.

DR. CHAVES: We have observed reducing substances in the urine of diabetics receiving all three major anti-tuberculosis drugs.

MODERATOR MC CLEMENT: *Or can any of these drugs interfere with glucose metabolism?*

DR. CHAVES: I am not aware of such an interference. Maybe some of the other members of the panel are.

DR. RILEY: It seems to me that a few years ago I read in the British Medical Journal of some case reports of elevated blood sugars following isoniazid. This, as I remember, was an isolated report of a few cases. I have never seen it followed up.

MODERATOR MC CLEMENT: Some of my associates who are interested in metabolic disease tell me that in cases of pyridoxine deficiency there are some abnormalities in glucose metabolism, and since with isoniazid one may get interference with pyridoxine metabolism it is conceivable that some alterations in glucose metabolism will be found. From a practical point of view, I think our experience indicates that if glycosuria is found in a patient under treatment, the most likely explanation for this is that this is glucose which is unrelated to their specific drug treatment.

The last question is: *How can we know that there is a cavity present?* We have spoken about "open negative cavities." *How can we know there is a cavity present if, in fact, the sputum is negative?*

Dr. Chaves, I think you are the one who used that phrase, "open negative."

DR. CHAVES: I used the phrase, but it was introduced in a paper by Corpe.[1, 2]

I think the best way is by serial x-ray examination. Most of us can recognize an obvious cavity in association with positive sputum, and as the sputum becomes negative we can see that this cavity may under-

1. Corpe, R. F. and Sturgis, I. "Open-healing" of tuberculous cavities, *Amer. Rev. Tuber. 75*:223, 1957.
2. Corpe, R. F. and Blalock, F. A. The fate of the patient with resistant cavitation and non-infectious sputum ("open negative") after discharge from the hospital. *Amer. Rev. Tuber. 77*:764, 1958.

go certain changes, but it remains obviously ring-shaped on the x-ray, and that would be a residual cavity. There are other ways of demonstrating residual cavities. For instance, one way would be by sectional radiography, where one can see a cystic defect at the site of the original lesion. In this situation it would be helpful to have a baseline tomogram. I think in many instances it is a luxury and unnecessary, but in these circumstances one wants to know what the residua are. One can deal better with the situation if one knows what the status was at the onset. Comparing sets of tomograms taken at the beginning and at the end of treatment can frequently prove helpful in determining whether a specific residual air space is a residual cavity, or an emphysematous bulla that developed, or a pneumatocele.

QUESTION: *Can there be a cavity due to another disease?*

MODERATOR MC CLEMENT: I think that this is a difficult question that does plague us at times. Particularly late in the course of treatment, we do find circular shadows on the x-ray film, and it is often difficult to determine whether these are or are not cavities. Even when one examines the removed specimens, it is often difficult to determine whether these are cavities, bronchiectatic areas, cysts or blebs. As Dr. Chaves has indicated, probably the best way to approach this problem is by a serial study and an understanding of how the disease evolves.

This concludes the panel session. I wish to thank the panel members for their contributions.

THE STORY OF HOPE HOSPITAL*

SAMUEL COCHRAN, M.D.

1871-1952

ABOUT 1896 or 1897 the Central China Mission of the American Presbyterian Church, North, asked the New York Board for two clerical missionaries to open an unoccupied field in Northern Anhwei, a region in which members of the Nanking Station had occasionally travelled. The prefecture was Fengyang, the birthplace of the famous Chu Hung Wu, the first Ming Emperor. It is a flat, fertile, farming country, very populous, through which runs a large river, the Hwai, with a sizable branch, the Go. At the junction of these is Hwaiyuan, a magistracy of 30,000 people, supported by the trade arising from the export of grain, beans, hemp, etcetera. It is about 140 miles northwest of Nanking. It was thirty miles from the main Nanking-Tientsin highway, a dirt road usable only by pack animals, wheelbarrows and coolies. Nevertheless, this road used to carry a heavy traffic in goods and along it were numerous inns, catering to those who travelled it. The heavier goods went up and down the Hwai River to the Grand Canal at Tsingkiangpu and so to the Yangtse at Chinkiang. In our goings and comings we got to Pukow in four days by foot, or on mule-back. If the ladies and children were to be taken, we went by Chinese "junk" by Tsingkiangpu; time, two to four weeks.

The Presbyterian Board replied to the request by appointing DuBois Morris and Edwin Lobenstine. Rose Lobenstine, Ed's sister, went at her own expense and without Board appointment. The entire support of the enterprise was assumed by the Central Presbyterian Church of New York, Dr. Wilton Merle-Smith, pastor.

The above missionaries reached China in September '98 and the

* This account was written by Dr. Cochran in 1948 for his four children, but was only recently made available for publication. The story graphically describes the trials and tribulations, and also the satisfactions, associated with the founding of a mission hospital in a strange land. It also gives an interesting picture of the medical problems encountered in China at the turn of the century.

Dr. Cochran was born in Mendham, New Jersey, on May 9, 1871. He received his A.B. degree from Princeton University in 1893 and his M.D. degree from the College of Physicians and Surgeons of Columbia University in 1896. He went to China in 1899 and left that country in December of 1925. He died in Newport, Rhode Island, on December 26, 1952, in his 81st year. (Ed.)

Mission asked for a physician to be sent out. My brother Jim and I had been accepted by the Board but we stipulated that, if possible, we should go to the same place. Morris and Lobenstine had asked that I should go to Hwaiyuan, if possible. Lobenstine's father, Mr. William Lobenstine, solved the problem by offering to support Jim and his wife, while the Central Church undertook the salary of my wife and me. Mr. Lobenstine also made an offer of $10,000 to build a hospital.

We four Cochrans reached China in September 1899 and spent the first winter in Nanking in language study. Morris and the Lobenstines also were there for their second year of language study. There was an ominous atmosphere in China (though we newcomers did not realize it, in our innocence), for the great Boxer storm was brewing, and skies were getting steadily darker. In June the Boxer disorders really broke out in full force and we all spent the next few months in Japan. We Cochrans got back to China in February, 1901.

Following the Boxer outbreak, China was unusually peaceful, tired out, no doubt, by the horrible tension. The way was open for us to go north. It was decided that the first party should consist of Lobenstine, Morris and myself, with Mr. William Drummond of Nanking as an experienced adviser and director. A house had been rented for us by a Chinese evangelist from Nanking. I was assigned to go by boat, taking some furniture, groceries, a moderate amount of medical supplies, some books for our own reading, and tracts and gospels for distribution. With me went my Chinese teacher, Mr. Fang Hsing Shan, and Mr. and Mrs. Lu Si Ts'ing and their infant; Mr. Lu was an evangelist. Lobenstine, Morris and I had assumed Chinese dress, had our heads shaved by a Chinese barber and wore queues pinned to our round Chinese caps. My wife looked on in horror as my locks (I had some then) fell before the razor. I then made my way to the san ts'ang kiang chw'ang (three cabin Yangtse boat) lying off Hansimen, and when I awoke the next morning we were on our way. The trip took exactly one month; the Chinese boat people were in no hurry, nor was I. My days were fully occupied with my teacher; we read the Sacred Edict, the Analects and Mateer's Reader, and talked and wrote Chinese. I slept on a Chinese pei wo (quilt) on the plank floor, by Mr. Fang, my teacher, the Lu family having the cabin. We had our (very) plain Chinese fare together. None of them knew English. In the evening I read Browning's Ring and the Book, The Inn Album, The Blot on

the Scutcheon, Bishop Bloughram's Apology, etcetera. The trip was a great introduction to China. Every moment was different as we sailed (shun feng) or tacked (ting feng) and watched the passing panorama of the Grand Canal and the Hwai River, with the market towns that lined their banks and the multitude of boats of all sizes, going with us or meeting us. I shall always be grateful for this experience. After reaching Hwaiyuan, I accompanied Mr. Drummond on a further trip of exploration, 120 miles up the Go River to Poh Chow, which was the limit of our field in that direction.

We had rented a small two-room shop, a mile away on the north edge of the town, across the Go River. In November I opened a small dispensary there. Things started, of course, in a small way, but it was not long before I realized that two diseases were extremely rife, both of which were causes of much misery and disability, yet which could be relieved with certainty by surgery. These complaints were entropion, secondary to trachoma, and vesical calculus. It was many months before any of the sufferers from calculus would risk an operation, but soon after beginning work I did a successful plastic operation for entropion, and thereafter they sought treatment in increasing numbers.

Our first big success came with the treatment of a case of opium poisoning. During my first winter in Nanking, I learned that this condition was very common, and I ordered from home a Fels-O'Dwyer artificial respiration set. Death from opium poisoning is usually due to inhibition of the respiration. The Fels-O'Dwyer set is a rather crude but entirely efficient means of keeping up breathing indefinitely. Our first case was a neighbor, and my Chinese student, Chu Hsien T'ing, and I spent a long night and much of the next day keeping the foot-operated bellows going. In the end the patient survived in good condition; he was just about gone when we reached him. We heard afterwards that a rumor went round that we had restored a dead man to life, which helped our reputation a lot. As a matter of fact, he appeared almost dead when we first saw him. I do not know how many scores of similar cases we treated in the following years, but I imagine we handled 20 to 25 cases a year.

Late in the spring of 1902 we were able to rent a larger property much nearer to us. The buildings were rubblestone-walled, thatch-roofed, and we put in brick floors. One we used as dispensary and operating room. Nothing could have been more unfitted for surgical

work; they were a horror to anyone used to ideals of asepsis. We had no pressure sterilizer and had to depend on fractional sterilization by flowing steam. But that is all that we had until we moved into our foreign-built hospital in 1910. Our equipment was almost as crude as our buildings. Our beds were merely boards laid on low wooden trestles and we had no furniture found in a modern hospital.

I shall never forget the morning clinic of one day soon after we moved in. A man from 90 miles away brought in his little boy, and gave the characteristic history of urinary calculus. I told him what was wrong and offered an operation, as I had to a number of others; instead of the expected refusal, he said, "All right, Doctor", and we sent him back to a ward. The next patient gave the same history and again, when offered operation, said "All right, Doctor". The third patient was exactly the same as the first two! You can imagine my astonishment and pleasure, after months of waiting to be able to perform the operation that would mean so much to them (and to us). It seems that the three came from one village and travelled together. After reaching Hwaiyuan they had waited for a week in an inn, making inquiries about our reputation, and getting divergent advice, some saying that we had helped eye patients and saved opium cases and some saying that they had better not trust themselves to the "Foreign Devils". All three cases had successful results and from then on we had an increasing stream of applicants. There are few conditions which can cause so much horrible suffering, and the relief is so immediate and complete that they go home eternally grateful to spread the reputation of the hospital, and with a knowledge of the Gospel that is often the beginning of a church among their neighbors. Gratitude for kindness seems to be an especially strong trait among Chinese. I shall digress to tell of a few incidents.

A few years ago, 20 years after I had left Hwaiyuan, I received a letter from there containing a portrait by a country photographer of a plain-looking farmer. The accompanying letter explained that the subject and owner of the photograph had brought it in. He had been operated upon by me for vesical calculus more than twenty years previously when a very small child, and he asked to have this picture sent to me. Also, "Would I send my own portrait to him?" You may be sure that I did. While at Tsinan, long after leaving Hwaiyuan, I had a patient come there to me, 300 miles, asking for operation; I saw

that he had the best that our University Hospital could furnish. Within the last few months, I have had, from Chinese physicians studying in this country, former pupils at Cheeloo, expressions of gratitude and affection that would warm any man's heart.

To return to the first year at Hwaiyuan. At the same time that those first three calculus cases were in the hospital, a man named Keng Ch'ang Ch'ing came in with opacities in the middle of both corneae, secondary to trachoma and entropion. He was a reasonably well-to-do farmer, the oldest brother and the head of the family, living 25 miles to the southwest at Keng Chia Ts'un, a small village. He could not see well enough to go about alone. I was able, by iridectomies, to make false pupils and to restore enough sight to enable him to get about freely and read good-sized print. Our evangelist was in the ward daily, conversing with these patients, but at first he paid little attention to the "foreign religion". By chance, there was a heavy rain the evening after one of the calculus cases was operated upon, but of course, as usual, I came down through the downpour, several city blocks, to see that the operation case was all right before I went to bed. For some reason, Mr. Keng was considerably impressed by the fact that the foreign doctor was willing to take a wetting for someone who was not his own relative. He began to listen to the evangelist, took gospels and tracts with him when he went home, and a few weeks later turned up asking for baptism. After a reasonable period he was baptized, and then other members of his family and his neighbors began coming also. Regular church services were started. From this first "colony", subcolonies began to appear in a widening circle, like subcolonies on a Petri dish. There are now hundreds of believers in that district. They have their own church and pastor (self-supporting). Every Sunday religious worship is held in a number of centers within ten miles of the Keng Village; I do not know how many (perhaps ten or more); some of them have their own places of worship; each has its Sunday School; there are several day schools and their own church elders; all started by the healing of Keng Ch'ang Ch'ing's eyes. As for Mr. Keng, he and I were friends who never forgot each other. I remember, with deep pleasure, weekends I have spent in his home, serving as lay preacher at the Sunday chapel services. He died several years ago. His nephew, George Keng, is now at Teachers College of Columbia University.

This was the case that seemed to start things going, but through

the years similar stories about sufferers coming from North, South, East and West, were developing.

Things went on like this from 1902 till 1910 (Chinese New Year) when we opened Hope Hospital. When we went out to China, Mr. W. C. Lobenstine told us that he stood ready to give $10,000 (U. S. currency) to build a hospital and we should have been glad to do this much sooner than we did, but no one would sell land.

Through all the years I was there, we were treated with courtesy and consideration. Of course, there must have been distrust and dislike on the part of many, for strangers like ourselves; xenophobia is a universal trait of mankind. How often we had "Yang Kwei Tsi"* called after us! But apart from this, we never once were hustled on a street or offered violence in the slightest degree. We have every reason to be grateful to the people of Hwaiyuan for the forbearance and kindness with which we were treated. Undoubtedly, our hospital helped a lot. We opened a boys' school (Jim Cochran ran it and he was always a friend-maker) and that made us friends. About 1906 there was a local famine and we gave out relief by providing funds and superintendence (Jim and DuBois) for the building of a river dyke. Nevertheless, it was several years before anyone would incur the odium of selling us land. Finally, about the Fall of 1906 we bought an old site from the Shansi Hueikwan (Guild). The guild had decayed and the buildings were no more, only some of the foundations. The remaining members of the guild were glad to get the money and were uninhibited by Hwaiyuan disinclination to sell to foreigners. Furthermore, no Chinese would think of living in it because, being a temple site, it was supposed to be haunted by "chi peh nien tih kwei" (hundreds of years of ghosts). We were not afraid of kwei and even the Chinese said that a hospital would exorcise them. And it was the very best site in town for the purpose, with a commanding position well above the recurring floods that plague Hwaiyuan, when people go about in boats. The building was started in 1907 and completed in 1909. Through 1908 I was at home on furlough, and with considerable hard work I raised $5000 gold for furnishing it. Some of it was given by generous members of my own family; John Stuart Kennedy gave $500 and one gift came from The Presbyterian Hospital Alumni Association.

We moved in just before Chinese New Year 1910 and had a formal

* "Foreign Devil"

opening. The district magistrate was the guest of honor and a large number of town notables partook with us of the best feast we could provide. We felt at last that we were established and accepted.

When it came to naming the hospital, Mr. Lobenstine, the donor, had a most happy inspiration. Hope Hospital it was called, which goes most fittingly into Min Wang I Yuan, a name known far and wide over North Anhwei. What a pleasure it was to have pressure sterilizers, a good laboratory, which included an incubator given by Dr. John Howland, acetylene light for the operating room, a Bunsen burner in the lab, Lawson Tait beds and our own bedding which could be kept immaculate!

I must not forget to tell about one man to whom I owe more than I can ever express, "Dr." Chu Hsien T'ing. He was the son of one of the early Christian women in Nanking and had had a partial medical course in the Methodist University in Nanking under Dr. George Stewart. He went up with us when we first went to Hwaiyuan and was with me, with the exception of one year, until 1917. He was called "Doctor" by courtesy, as he never attended medical school and he learned by the apprentice method, as many a practitioner did in the early days of the profession in America. All that he knew of medicine he learned from me, partly by studying the scanty text-books then available in Chinese, and mostly by the daily work of the hospital. He could do an excellent plastic on the eyelids for entropion and an equally good suprapubic cystotomy for calculus. His outstanding characteristics were a thorough knowledge of Chinese "customs" and social contacts, a large fund of common sense, an awareness of what was going on, a dignity in dealing with high and low, District Magistrate to kitchen coolie, and an unfailing faithfulness and loyalty. He saved me from more mistakes than I shall ever know. To him be the credit for whatever success we had in becoming established in the esteem of the community, and for keeping the hospital running without friction or scandal. He always had the respect and cooperation of everyone in the hospital and community. He left us for a year, 1910-11, and came back to us because I persuaded him that we needed him. I shall never forget the day he arrived back, one afternoon in November while I was operating. It was the day of a cold wintry tempest of rain and wind. Travel by road was dangerous, as the 1911 revolution was on and there was temporary anarchy—"The good old rule the simple plan, That those should take who have the power

and those should keep who can." His boat was laid up by a town ten miles away and he walked in through the cold storm, in a ragged shirt and slacks. To wear anything better was to risk being plundered and murdered. And were we glad to see him!

The great revolution reached us about November 1st, 1911. As it came closer and closer, disorder and danger increased. Finally it seemed wise to send our ladies and children to Shanghai under the escort of DuBois Morris. Mr. Gray and I stayed to hold the fort. Finally the t'u fei (local rowdies) ganged up on the town to the number of several thousand and an attack, with inevitable looting and massacre, was imminent. I shall never forget the afternoon when the Revolution reached us, after several exciting days of rumor and disorder. I stood on the upper veranda of the Boys' School and saw the white flags of the revolution go up by scores over the roofs of the town. After a day or so, two Chinese friends (literati of position in town) came to us and told us that the sack of the town was imminent and urged us to leave for Nanking, as our presence could be of no service and they feared we might suffer violence. They brought with them a man who, they said, could see us through safely, as he was a member of the Triad Society and had passwords that he could use with Triads along the way. It was not an attractive journey, as all bonds of law had been dissolved, but it seemed wise to do it, or less foolish than to stay. Dr. Chu agreed to stay and keep the hospital running, as all the Chinese staff trusted him, and his presence would give them courage (a little of it at least). We went by our motor launch to Lin Hwai Kwan, 30 miles down river, and spent two nights there. On the morning of the second day we heard at the railway station that a train was coming through from Pukow bringing the Chief Engineer, a Mr. Tuckey, on a trip to learn conditions (trains had not been running for about a week). We went with him up to Pengpu, the nearest station to Hwaiyuan, and there I found a messenger with a letter from Dr. Chu, saying that the t'u fei had attacked the town the very night that we had left and had been beaten off by the people who had rallied around the magistrate and his yamen runners. The magistrate had been wounded and was in Hope Hospital, and Dr. Chu asked that I return and treat him, which I did. It seemed best for Mr. Gray to go back to Pukow with Mr. Tuckey. When I arrived at Hwaiyuan I found that the magistrate had merely a flesh wound of the thigh and he did well. Another patient was Yang Ta Ya (Big Tooth

Yang), one of the t'u fei leaders. I stayed for another week or ten days and then a message came from our consul asking me to come away, which I did, by train. I stayed in Shanghai till the last week in December and then returned by train to Hwaiyuan. There I found everything quiet. Not a particle of damage had been done to any of our property and the buildings had not been entered. I heard from Chinese sources that word had been passed around among the t'u fei that no harm was to be done to the foreigners nor their property because of the famine relief that we had given out and because of the good work the hospital was doing for the country people.

The next few months were passed in an unusually friendly atmosphere. Attendant on the delivery from the Manchus, a wave of pro-democratic feeling swept the country; the queue disappeared overnight, the magistrate was not addressed as Ta Lao Yeh ("Your Honor") but sienseng ("Mr."); America and American customs and citizens were popular, and considerable of the prejudice against Christianity disappeared. Church services had large attendance.

For the first years at Hwaiyuan I was the only physician there and my nearest neighbor in the profession was Dr. Osgood of the Disciples Mission, at Ch'u-chow 90 miles away towards Nanking. There was no trained nurse till Rose Hoffman, an especially fine graduate of Presbyterian Hospital, New York, came out in 1903. Alas, she was married after one year, to Lobenstine; next year a baby arrived, and in 1908 she died while another baby was on the way. She was deeply mourned by us all, and her death was a great loss. One of the really major problems of mission hospitals is the terrific loss by marriage! I should hate to try and count the number of nurses Hwaiyuan lost in this way after brief service. A lone physician in this situation has to be doctor, oversee what little can be offered in the way of nursing, and act as hospital superintendent, which includes keeping all the accounts, engaging employees, including the cooks, instructing untrained assistants in dispensing drugs, doing laboratory exams and giving anesthetics; he has to order drugs and supplies and be his own public relations man; he must care for his own family when ill and welcome his own children into the world. Finally, I drew up the plans for our new hospital, negotiated the contract and did much of superintending the building (I was on furlough for part of the time while the hospital was going up and Mr. Lobenstine did the overseeing). One had to treat patients in most of the specialties,

in addition to general medicine and surgery; among other things, I did a good many cataract operations. It goes without saying that no man could possibly do all these many things with top skill. Nevertheless, many lives were saved and much suffering was relieved; many friends were made and to the poor the Gospel was preached. For a time I was Sunday School superintendent and, believe it or not, I often played the organ for Sunday Church services (please do not think I am trying to make myself out another Schweitzer; I simply did what came along even if I could not do it well).

In 1908, Mary, Agnes and Margaret Murdoch came out and what a difference that made! No finer missionaries ever came to a mission station. Agnes and Margaret had excellent training, Agnes as physician at Johns Hopkins, Peggie as nurse at St. John's Dispensary in Baltimore, and Mary as an evangelist. They combined a high degree of medical skill with warm, attractive personalities and a rare unselfishness and kindliness. Throughout their long service everyone, Chinese and foreigners, became their friends. It was a rare privilege to work with them and to have their help. Perhaps their finest achievement was their foundling service, which during their many years rescued well on to 200 babies. For most of them they found foster mothers. A number they adopted as their own daughters and gave them education as nurses or teachers. To me, it was the finest piece of work of which I have any knowledge in China. It was greatly appreciated by the Chinese public, who turned over to Margaret a small temple which she used to house the little ones till they were handed over to foster mothers.

The Murdochs came in time to get Hope Hospital in order, and under their womanly care medical work moved forward on an entirely new plane. Every department of the work was improved.

During my first furlough in 1908 I took a three months' course at the London School of Tropical Medicine, going over with Dr. Sidney Lasell and sharing quarters with him in dingy diggings down along the docks. It was abundantly worthwhile and gave me my start in a more scientific approach to diseases prevalent in China. For one thing, I became aware that I had probably been seeing a lot of Leishmaniasis, a disease of which I had not yet heard. Also, I became interested in intestinal helminths and, with a fairly equipped laboratory, I could teach my students the necessary microscopic examinations. I brought back an incubator when I came, the gift of Dr. John Howland, later Professor

of Pediatrics at Johns Hopkins.

The first years at Hwaiyuan were spent in marked geographical isolation. We were four days by "han lu" (overland) (you traveled on foot or on donkey or mule; once or twice I made the trip with my wife by sedan chair; once or twice I rode on top of a mule-load of merchandise). There was no post office for two or three years, and we hired our own two couriers who brought the mail once a week from Nanking. About 1903 the Chinese Imperial Post opened an office in Hwaiyuan, the mail coming by courier from Nanking. With the establishment of the postoffice the Chinese began reading the Shanghai Chinese newspapers and there was a new interest in national and international affairs. This spreading of information throughout China by a general opening of postoffices undoubtedly hastened the Revolution of 1911.

The building of the Tientsin-Pukow Railway was begun in 1908 while my family and I were on furlough. While I was in America a medical friend was telling me at a dinner about his interest in caisson disease, which he was treating as surgeon for the East River tunnel in New York City. Mentally, I paid little attention, saying to myself, "This is something I surely do not have to bother about". In February 1909 on my way back to Hwaiyuan with wife and children on a Chinese boat, our last stop overnight was on the bank of the Hwai at Pengpu eight miles from home. We had a caller, a Mr. T. J. Bourne, who soon became a warm friend. He was district engineer for the Tientsin-Pukow Railway, which planned a big bridge at Pengpu. Mr. Bourne asked if I would be willing to serve the railway staff, foreign and Chinese, as surgeon; I agreed to do so insofar as possible, without compromising my obligation to Hope Hospital. "You may have to treat caisson disease," he said! This was the beginning of a long friendship with Mr. Bourne and his family, who lived for two years at Pengpu and whom my daughter Peggie and I visited in their home near Southampton in 1927. For years we had very cordial relations with the T. P. R. staff, who visited us in our Hwaiyuan homes. One of them spent several weeks as guest of my brother and his wife, recovering from a broken arm. We had a considerable flow of patients, mostly traumatic cases, from the railway construction force. At Bourne's request I obtained copies of a little book, *The Care of Health in the Tropics*, prepared by one of the lecturers at the London School of Tropical Medicine. This I had interleaved with typewritten emendations to make it completely applicable to Chinese

conditions. Among pieces of advice included was a warning that lice might carry typhus. This was very recent up-to-date information, based on Rickett's studies in Mexico. Little did I think how very urgent this matter might soon become to all of us.

The summer of 1910 saw a terrific rainfall in our part of China. It came down in buckets in July at Kuling, where I was finishing my vacation. When a few days later I got back to Pengpu the whole country was a vast lake. The railway staff kept a daily record of the precipitation and on two successive days it was 16 inches, 32 inches in 48 hours! Three inches a day is about the top record for New York. The rivers burst their banks. The wheat harvest in June was mostly in the homes of the farmers and was destroyed, as water was feet deep in the houses and many of them had tumbled down. Furthermore, no fall crop could be harvested, except possibly a little late buckwheat, which ripens in six weeks from planting. A famine, and a bad one, was inevitable, and I think that the first warning of this was in my dispatches to the "China Press" of Shanghai, of which I was a local correspondent.

As the months passed we could see the spectre of famine coming nearer. It was well publicized and an active and efficient famine relief organization was formed in Shanghai, with Mr. J. C. Ferguson as president. One of the American religious journals carried publicity for the Committee and large sums were raised (something like $2,500,000 U. S. gold, I believe). A considerable staff, largely missionaries, oversaw the transportation and distribution of rice brought from Wuhu. This was THE big famine so vividly described in "The Good Earth", book and film. No description can give an adequate picture of a disaster like this. One has to see it (and smell it) day by day. Refugees trekked south by the hundred thousand, some with wheelbarrows and household goods. They did not jam the roads, as in The Good Earth film; they did not have to. A group here and there, over a wide area and over several weeks' time, will carry millions to camp in the temples and in huts outside the Nanking, Soochow and Chinkiang walls.

The streets were full of starving people of all ages and both sexes, the temples were jammed with refugees, for whom our local chamber of commerce gave a little token relief in the form of a rice kitchen. Pretty soon the Chinese head teacher of our boys' school was admitted to the hospital with typhus. I was asked by the Chamber of Commerce to inspect some of the temples. What I found was indescribable; hun-

dreds gathered together, with no fuel against the winter cold and, worse, no hot water for washing garments and filthy bodies. There were scores lying ill with fever in miserable filth, and most ominous of all, the floors were alive with lice. I was unable to give any useful advice or any help. There was simply nothing practical for one to suggest, with such a multitude.

Nothing worth mentioning was possible for these refugees. What was done was to provide rice for the starving country and city people in their homes. The railway was by this time constructed as far as Lin Hwai Kwan on the Hwai River, 30 miles away, and rice was shipped there from Wuhu, and from Lin Hwai by native boat. Lists of starving were made in each of 40 of the worst stricken of the Hwaiyuanhsien 104 wards. These lists were handed in by the constable of each ward. Tickets were distributed to those on the lists and they came in to town and were given a fixed quantity of rice for each ticket. Gradually other neighboring hsien were included in the distribution and hundreds of thousands of lives were saved.

There were several distributing centers in different magistracies. Hwai Yuan was a supply base for the volunteers who were giving out relief, and canned goods and other edibles had to be sent out through us.

As mentioned above, a good deal of the relief was supported by remittances from America. We had as neighbors in Hwaiyuan a French Catholic Mission with whom we were on very friendly terms because of our hospital. Scattered through the region were other Catholic stations. I was at first the local treasurer for the famine relief committee and had some discretion in providing relief. I heard that the Catholic missionaries were getting no money from France and some of their Christians were starving. I was able to send means of relief to Father Hermann, their superintendent, for the Hwaiyuan region. I received a most beautiful letter in French from him saying that masses were being said for my benefit in their churches, which touched me very much, even though I knew I had acted only as the agent of others' generosity. Two months later, the good Father died in our hospital of typhus.

Early in March I made a trip of three days around the wards where distribution was being made, in order to size up conditions. Mr. Pettus, later of the Peking-Language School, went with me. We saw pretty grim conditions and it appeared that the constables had been too rigid in their criteria of what constituted need of relief. Pettus and I got back

after a long ride (mule-back) in the rain, with me feeling chilly and aching. I went down to see the Chinese head of the Chamber of Commerce, and authorized him to loosen up a bit and be more generous in the classification of those needing relief. In the evening I stayed home from the church mid-week meeting and balanced my Famine Relief accounts. The bank account contained about $40,000 Chinese currency, as I recollect, which shows that operations were already carried on in a fairly large way. Then I took a hot bath and toddy for a supposed "cold". The next two weeks are a blank in memory, except for some very bad dreams. I never would have pulled through but for the devotion of Agnes and Peggie Murdoch, Robert Beebe, Phil Evans, Randolph Shields, not to mention my wife and brother, all of whom, with others (Dr. Chu for one), lent a hand at the nursing. How grateful I am to them! It is to be remembered that typhus was then supposed to be very contagious.

DuBois Morris had returned from furlough with his bride, Alice Buell Morris, a few weeks before I was taken ill. He and my brother and I had conducted a house-to-house census of Hwaiyuan city to enroll relief applicants, and it may have been during that canvass that I contracted typhus. DuBois also came down a few days after I did and we lay in adjoining rooms, both desperately ill and cared for by the above-mentioned friends, plus several volunteer missionary nurses from stations of our own and other missions. After recovery it was several months before either of us was well enough to work, and when we got back to Hwaiyuan in the fall, the Revolution came on, as described on previous pages.

While we were ill there was a general epidemic of typhus and relapsing fever. We heard of at least half a dozen deaths among mission personnel in different places; two of the French Catholic priests died in our hospital. Some of our Chinese staff were ill, including our good friend, Liu Chioh Fei. Dear man! While DuBois and I were ill he said in a sermon in our church that getting typhus was due to "a lack of faith". Alas! Shortly after, he came down himself.

The famine continued on a milder scale during the Fall, Winter and Spring of 1911-12 and further relief was conducted in our area. Also, the epidemic of typhus and relapsing fever recurred. During the Spring of 1911, while we were ill, it was not possible for Hope Hospital to try to cope with the epidemic, but in the spring of 1912 we operated a

special fever ward in some adjacent Chinese buildings, treating about 120 cases, 90 of relapsing fever and 30 of typhus. The mortality was low and it seems likely that the Chinese have a higher immunity to typhus than do Westerners, among whom the death rate is very high. Relapsing fever yielded promptly to arsphenamine, but we could not afford to buy it for more than a few cases, at the current prices.

After returning to Hwaiyuan in 1909 and opening Hope Hospital, I began to investigate the splenomegaly cases of which we saw so many. The symptom-complex and blood counts pointed strongly to leishmaniasis, but of course the diagnosis could not be complete without demonstrating the Leishman-Donovan body. I searched long hours through blood smears, without results. Splenic puncture would have settled it quickly but I did not dare use it, for there was a bad history of fatal hemorrhages in a number of cases (two of them in a mission hospital in Shantung). Finally I excised an inguinal lymph node under cocaine and found Leishmania in astonishing profusion. I mailed a slide to Dr. Daniels, head of the London School of Tropical Medicine. He wrote back very cordially, confirming the diagnosis, expressing interest in the technique and enclosing a cheque for 50 pounds sterling, to finance further study. Part of it I used in circulating a questionnaire to a considerable number of hospitals in China and obtained a satisfactory response. In the end I submitted an article to the School, detailing the histories and observations on a series of cases, together with a map showing the endemic area as outlined by the questionnaire. The article was published by their journal. The endemic area is now known to be somewhat larger than I was able to report, as Dr. Hou Pao Chang has found it out in the West of Szechuan. The use of lymph nodes in diagnosis was followed by us for some time. Later, I shifted to using liver-puncture, which is safer than spleen-puncture and just as useful.

Though we now know how to diagnose kala-azar we were no further along in its treatment. It is stated that the mortality, unless treated by antimony, is 95 per cent and I quite believe it, though we saw most of our cases only once or twice and can offer no statistics. Sometime during those years, perhaps 1915 (I was on furlough in 1914), I decided to try splenectomy because one of my journals told of one case of kala-azar so treated in Athens. It proved to be a valuable procedure, the patients improving in a very striking way immediately following the operation. The operation is a serious one and may be quite difficult, as

the spleens are enormous, weighing several pounds and sometimes bound by adhesions. The blood vessels are huge and tear easily. I did thirteen splenectomies with no fatality at the time of operation, though two of them died while still in the hospital. The others did well and there were several apparent "cures". I felt that I had discovered something that might prove of general value, but just then the discovery of antimony as a specific for Leishmania infections was made in India. No one was more glad than I when the whole picture changed, and instead of possibly five out of 100 surviving, less than five out of 100 died, and those because treated too late. Of all drugs in our armamentarium, antimony is certainly the winner by a wide margin, in its own particular field; it is more dependable than the anti-malarial drugs in malaria, or arsenic and bismuth in lues. I should say that there are more failures in the use of penicillin than there are of antimony in kala-azar. For many years we had seen these big spleens file through the O.P.D. and had done nothing for them but give some quinine as a placebo. Now these children (most of our cases were in young people) came to us wrecks, with yellow, woebegone faces, and after a few weeks of treatment went home happy and smiling. I believe that Hope Hospital, just before the Japanese invasion, treated over 1000 cases a year.

My interest in laboratory medicine continued to grow and during my 1914 furlough I took a course in bacteriology and serology at Post Graduate Hospital, New York, under Ward J. MacNeil. It was an excellent course and the time spent was very profitable.

During these years one or two feelers had come to me as to whether I would be interested in going into medical teaching. Two were from Peking (one from Cormack, I think, and one from Roger Greene). Also, I was approached by the medical school at Cheeloo, but I always felt that I had a well worth-while job to do at Hwaiyuan and hated to leave when things were manifestly going well, to attempt something for which my fitness was not demonstrated. Finally, they sent a request from Tsinan to our mission that I be loaned for one teaching year to give the course in Laboratory Diagnosis and in Bacteriology. The answer was favorable and I spent the winter of 1917-18 at Tsinan, my family staying in Hwaiyuan. I lived with the Shields and a delightful home it was. That winter was the one in which pneumonic plague broke out in Suiyuan, North of the Great Wall, and a Plague Prevention Service was organized under Dr. Ch'en S' Pang, a Cambridge graduate.

Roger Greene was on the committee and he wrote to me asking me to join the service, which I did. I went up with Ch'en by rail to Tatung in North Shanshi where there was a local epidemic. Smyly of the Peking Union Medical College was there, in charge of an isolation hospital. From there we went back to Kalgan, where several inns had been rented to use as an isolation hospital. I was put in charge of this, and Ch'en went back to Peking. I was there about two weeks when a telegram came, directing me to proceed at once to Feng Yang, near Hwaiyuan, where a small local epidemic had started, as the result of a victim from Suiyuan getting through the quarantine. When I arrived I found that the situation had been capably handled by the local magistrate, who had seen service in the 1911 big epidemic. The outbreak, only four or five cases, was over, but again a wire arrived, this time from Tsinan where two or three cases had appeared, off-shoots from Feng Yang. On arrival I found an explosive situation. It was at about the time of Japan's menacing attitude which was manifested in the famous "Twenty-one Demands" and Japan was sending down military officers from Peking to Tsinan, with bacteriologists from the Kitisato Institute of Tokyo, to make sure that the plague cases did not become a general menace. Locally, a plague-prevention organization was formed, with Chinese officials, the local consuls and members of our faculty included. Believe it or not, I was their chief (and only) technical dependence and had to make most of the decisions. A course at the London School of Tropical Medicine, 12 weeks with MacNeil in New York, and two weeks by myself at Kalgan were the sum of my qualifications. At least I had plenty of authority, for the Japanese menace made Chinese officialdom jittery and they did anything I asked. For one thing, at my direction they stopped passenger traffic on the Tientsen-Pukow Railway until I said it could start again, and I remember well the advertisement in a Tientsin newspaper announcing that on permission of Dr. Samuel Cochran sale of tickets would be resumed. (I wish that I had kept a copy of the paper!) We had a number of meetings with the Japanese deputation, including an inevitable dinner, during which a messenger brought a note to the Japanese consul saying that there had just been a death which the Chinese had concealed. It was a tense moment, the Chinese officials looking very shame-faced and alarmed. I at once asked permission to exhume the body and make cultures and was granted my request. Next day, with a lab assistant, I went out accompanied by officers from the

yamen, saw the grave opened and put an exploring needle into a lung and made cultures. They grew out abundant bacillus pestis.

Our committee established an isolation hospital under charge of Dr. Gillison, but no more cases occurred. There is no evidence that our activities stopped the epidemic. It just stopped because winter was over and the weather was warm. However, we served the very useful purpose of restoring confidence and of checking Japanese interference. It made friends and was worth while. If I remember rightly, the Chinese Government gave me a Kia Ho medal and the American Minister sent me a letter of thanks. Also, the Managing Director of the T.P.R., so far from bearing a grudge, sent me $400 Mex (which I turned over to Hope Hospital), and a "pien" written by his brother, President Hsu Shih Chang.

The winter's work was most enjoyable. I saw at first hand the good work the school was doing and began to think I could at least get by as a teacher. So when I was asked to join the faculty I agreed, if the transfer could be arranged with my mission. My mission agreed but stipulated that I spend the winter of 1918-19 at Hwaiyuan. The next year I was due to have a furlough and the faculty advised my spending it in the study of bacteriology.

The next year, 1918-19, the work was heavy and towards the end I developed a cough. At Kuling I had a medical examination and Drs. Venable and Barry threw out a suspicion of T. B. So home I went, tagged as an invalid. At all events I got a fine rest lying in bed on the "rest squad" at Trudeau. It was a *delightful* three months, fine air, good food, plenty to read and feeling stronger every day. Trudeau turned me out with the opinion that I did not have T. B. at all and was unlikely to get it. It was a thoroughly satisfactory experience.

When I got back to New York I sought the advice of Simon Flexner, Director of the Rockefeller Institute, whom I had met when he was on a tour in China with "Popsie" Welch, of Johns Hopkins, about 1915. He suggested that I study with Hans Zinsser of Columbia University and offered to give me an introduction, which he proceeded to do over the phone in terms much more complimentary than accurate. I then went across town to the College of Physicians and Surgeons, then on 59th Street, and Zinsser gave me a teaching position, without pay. It was the beginning of a warm friendship with that talented and admirable man. He gave me plenty of work and the responsibility of

handling a laboratory course in immunology for graduate students. I could not have put in the year in more valuable fashion. For one thing, I served as demonstrator in the regular medical undergraduate course in bacteriology. In my following years I gave our Cheeloo students a course practically identical with that which the good Professor Hans gave the P&S students.

I returned to China directly after January 1st, 1921, and, after packing our household goods in Hwaiyuan, reached Tsinan in February in time for the opening of the Spring term. Soon after our arrival news came of a new outbreak of pneumonic plague. This time the Central Chinese Government set up an efficient prevention service under a Chinese public health man whose name I have forgotten. He had a considerable and competent staff, and the epidemic was a small one and did not reach Tsinan. It affected several magistracies 30 or 40 miles to the north of us. I was twice called to go to render help, and on one occasion the Director and I went into a house and took a blood culture from a man moribund with plague. The procedure required extreme precautions on our part for self-protection, and it was one of the most eerie experiences of my professional life. The cultures grew out many colonies of bacillus pestis. A week or two later the Director himself made a slip of technique in not being careful in examination of a suspect, caught pneumonic plague and died.

My years at Tsinan were happy ones indeed, but there is little to record about them. I was dean from sometime early in 1922 (I forget just when) till we left in December 1925. For a short time I was acting president of the University in Balme's absence. One thing which I recall with satisfaction was proposing, and assisting to put through, an amalgamation with the Women's Medical College of Peking, a proceeding which greatly strengthened both schools.

As I look back on the years between 1899 and 1925 it is with a realization that they were very happy ones. I am sure that nothing else that Margaret and I could have done would have proved so satisfying. Where else would we have had such friends and colleagues as at Hwaiyuan and Tsinan, Kuling and Peitaiho? What other place could have given us greater opportunities for useful and reasonably successful work?

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

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Morphology and Pathogenesis of Maturity Onset Diabetes

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In human diabetes mellitus there is not always demonstrable pathology of the pancreatic islets different from that of the non-diabetic pancreas. In many instances this may be accounted for by the fact that the diabetic syndrome is secondary to hyperfunction or tumors of the anterior pituitary, the adrenal cortex or medulla. However, that would still leave many cases in which there is no definite morphologic basis for the metabolic disturbance. The recently introduced hypoglycemic sulfonylureas contributed to a better understanding of the functional disturbance in human diabetes. These drugs which act primarily by stimulation of β cells to increase insulin output show their greatest effectiveness in maturity onset diabetes. This led to the conclusion that in these individuals the β cells do not respond adequately to the normal insulinogenic stimulus, which is hyperglycemia. Theoretically, a failure of β cell stimulation by hyperglycemia may be due to a defect in the β cell mechanism for the release of insulin, or, alternatively, it may result from difficulty in glucose transport to the cell. In the latter case, the glycemic level would not accurately represent the availability of glucose to the β cells. This could result from impairment of blood flow to the pancreas or from an impediment to the exchange of nutrients across the capillary membranes.

The present study was carried out in order to reevaluate the morphologic changes in the pancreas of diabetic patients not only in terms of reduction of islet tissue, but also in respect to additional changes which might reduce glucose availability to β cells. It was carried out on the pancreases of 50 diabetic patients of either sex, whose age ranged from 48 to 85 years, and of 50 non-diabetic individuals of similar age and sex distribution. The onset of diabetes was past the age of 40 and the duration of the disease varied from 2 to 25 years. Both the diabetic and non-diabetic individuals were usually afflicted with arteriosclerotic or hypertensive cardiovascular, cerebral or renal disease, or combinations of these conditions, as well as occlusive arteriosclerotic disease of the lower extremities.

The diabetic pancreases frequently showed varying degrees of atrophy and perilobular or interacinar fibrosis, with the latter the predominant variety. Although non-diabetic pancreases also showed considerable fibrosis, this was usually not so severe as in the diabetics. This latter group frequently also showed peri- and intra-insular fibrosis. The islets were in many instances traversed and distorted by fibrous tissue, which formed pericapillary bands. Varying degrees of hyalinization of islands were found in approximately 25 per cent of diabetics as contrasted with mild hyalinization in only 4 per cent of non-diabetics. Both insular fibrosis and hyalinization were focal in distribution and varied markedly in extent in individual islets. The same pancreas usually also showed comparatively intact, well-granulated β cells. Sixty per cent of diabetic pancreases revealed thickening and

hyalinization of arteriolar walls with narrowing or even almost complete occlusion of the lumina. On the other hand, only 34 per cent of non-diabetic pancreases displayed arteriolosclerosis, and even in these cases it was of lesser severity than in the diabetics. Furthermore, the diabetic pancreases showed, in 52 per cent of instances, varying degrees of occlusive arteriosclerosis, as compared with less severe arteriolar changes in 34 per cent of the non-diabetics.

The cause of fibrosis in the pancreas is frequently obscure. The perilobular type has been thought to be associated with duct obstruction. In these instances, the islets are usually spared. Interacinar fibrosis is thought in some instances to be due to chronic pancreatitis. In our series, infiltrates of lymphocytes and plasma cells in the proliferating fibrous stroma suggestive of an inflammatory etiology were encountered in 16 per cent of diabetics as compared with 6 per cent of non-diabetics.

These causative factors still do not account for the vast majority of cases of fibrosis. It has been held that atrophy of the pancreas with loss of both exocrine and endocrine parenchyma may result from ischemia. Also, the progressive increase with age of pancreatic fibrosis has been thought to implicate vascular factors in its etiology. Furthermore, focal pancreatic atrophy with fibrous replacement has been attributed to vascular lesions. The regular association observed in the present study of hyaline arteriolosclerosis with interacinar fibrosis, and with insular fibrosis and hyalinization, suggests a pathogenetic relationship between the arteriolar and the pancreatic lesions. The presence of severe degrees of arteriosclerosis and, in occasional instances, even occlusion of large pancreatic vessels associated with marked parenchymal atrophy and fibrosis, also implies a cause and effect relationship.

Although loss of β cells due to severe islet fibrosis, hyalinization, or both, would be sufficient in many instances to explain the etiology of diabetes, the causative factor in many pancreases with numerous residual well-granulated β cells remains to be elucidated. Since β cell granules indicate good reserve of stored insulin and adequate insulin synthesis, their presence indicates that there is no particular interference with these processes but only with insulin release. The rate of liberation of insulin from β cells has been shown to be directly related to the blood sugar concentration. The factor more directly involved is the availability of glucose-6-phosphate for β cell metabolism, which is in turn dependent on the glucose concentration in the surrounding tissue fluids. The development of diabetes could be explained on the basis that impaired blood supply to the islets results in lesser availability of glucose to the β cells than is represented by the blood sugar level. Under these circumstances, the milieu of the β cells of the maturity onset diabetic may be equivalent to that of the normoglycemic individual despite the elevation of vascular blood sugar concentration. This would permit a supply of nutrient material and glucose adequate for β cell viability and insulin synthesis and storage, but the stimulus to insulin release would be lacking. On the other hand, this impairment of vascular supply would not prevent the pharmacological β cell stimulating action of the hypoglycemic sulfonylureas. The present study suggests that impaired availability of glucose to β cells could be caused by arteriolosclerosis, arteriosclerosis, or both, as well as intra-insular pericapillary fibrosis or hyalinization. An analogy can be drawn between this hypothesized vascular mechanism for functional impairment of the endocrine pancreas and that for the development of hypertension and renal insufficiency. These may variously be due to lesions of the renal arteries, the arterioles or the glomerular capillary walls. The main reason for the lack of close correlation between the various pancreatic vascular lesions and the development of diabetes could be the fact that the pancreas, in contrast to the kidney, is not a vascular end organ.

DISCUSSION

JAMES I. BERKMAN: If I understand correctly, the authors propose that maturity onset diabetes follows the development of arteriolar disease of the pancreas. All of us who have been interested in diabetes have been concerned with the problem of

the allegedly normal pancreas, and more particularly those cases with normal islets with normal β cells. There have been some advances in recent years; with the introduction of new methods, including the techniques of specific granule stains and of insulin extraction, some of these normal pancreases no longer seem to exist. I would suspect that even in Dr. Volk's laboratory, a considerable number of patients with maturity onset diabetes have nothing by way of degranulation. I cannot believe that all the patients that were studied have the degree of vascular disease which was seen or demonstrated this evening. I wonder, too, and I think one gets a little pained with this question, which comes first in these patients, the diabetes or the vascular disease, and their association with hypertension. Certainly the extent and severity of vascular disease of the pancreas, as we have seen demonstrated, is considerably higher in the diabetic population than in the general population. This presentation brings up for discussion the significant number of patients with pancreatic arteriosclerosis with or without islet hyalinization who do not have diabetes. Some years ago Moschcowitz[1] proposed an alternative explanation for maturity onset diabetes, also based on pancreatic vascular disease. He suggested that arteriolar sclerosis with extension into the capillaries of the islets interfered either with the production of insulin or its liberation. This is an alternative explanation to the one given this evening that the hyperglycemic stimulus to insulin production or release from the pancreas is involved, rather than the direct effect of vascular insufficiency, on the production of insulin. I think this whole area, and even the concept that the alterations in islets we have seen here in diabetes have anything to do with the causation of the disease, is of considerable interest to most of us. I wonder whether Dr. Lazarus or Dr. Volk would be willing to express further how far they are willing to go in attributing a causative effect to the pancreatic vascular lesions in diabetes, and I refer obviously to the group of diabetics with the proper genetic background for their diabetes.

SIDNEY S. LAZARUS: I think Dr. Berkman's question rather precisely pinpoints the problems which are involved in the study I presented. Before these pancreases were examined, it was suggested from evidence derived from other studies that the problem in maturity onset diabetes was a lack of response of the β cells to their normal stimulus, which is hyperglycemia. This idea was advanced during the course of work with the hypoglycemic sulfonylureas, in which it was shown that these drugs degranulate the β cells, which is a sign of stimulation to increased output of insulin. This finding, as well as the clinical status and the age distribution of patients who respond to this drug, suggested that they would have fairly normal islet cells and quite good residual β cell function. Certain ideas have been advanced by others to account for diabetes in instances where the islets are fairly normal. One investigator suggested that there is thickening of the islet capillary basement membrane which interferes with the output of insulin from the β cells. Another worker thought that diabetes of maturity onset type may be a consequence of reduced blood flow to the pancreas due to arteriolosclerosis, which somehow interferes with the production of insulin by the β cells. These views are negated, however, by evidence that these pancreases are synthesizing and storing insulin at an adequate rate, as indicated by β cell granulation and pancreatic insulin content, which do not differ particularly from that found in non-diabetic individuals of the same age group.

In previous work, it was shown that glucose-6-phosphatase is present in β cells. From this and other histochemical studies, it was concluded that the output of insulin depends on the concentration of glucose-6-phosphate within the β cells, which will in turn depend on the amount of glucose which is present in tissue fluids surrounding these cells. This finding, when integrated with the morphologic evidence, seems to offer a solution to the problem of a diabetic patient with a pancreas containing a lot of insulin and good β cell granulation. It seems most reasonable that the high blood sugar concentration is not stimulating the

β cells to put out insulin, because the vascular and insular lesions prevent access of glucose to the β cell. In some instances, there may be a barrier between islet capillaries and β cells due to pericapillary fibrosis or hyalinization, but vascular disease of the pancreas probably is a more frequent cause of the reduced availability of glucose to the β cells. In support of this latter idea are the observations that frequently diabetes follows as a consequence of hypertension; and that arteriolosclerosis, which is a focal disease, appears in the pancreas in approximately 50 per cent of cases. Opposition to this viewpoint might be based on clinical impressions that vascular disease is a complication of diabetes and not an antecedent process. However, the clinical observations refer to arteriosclerosis and retinal vascular changes and not to arteriolosclerosis. Furthermore, due to the focal nature of vascular disease, clinical statistics lose significance unless the opportunity arises to correlate them with morphologic findings.

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The Vascular Basis for Hemorrhagic Pancreatitis in Dogs. Hourly Observations and Results of Calibrated Microsphere Injections

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Despite 50 years of ingenious experiments, the etiology of acute hemorrhagic pancreatitis remains obscure. The fact that the lesion has been produced by many different techniques has added to the perplexity of the problem.

Previous work from this laboratory[1-4] has produced experimental and clinical evidence to suggest that regardless of the initiating factor or factors, the final common pathway in the causal genesis of acute hemorrhagic pancreatitis is a vascular lesion. The experimental work that was reported from our laboratory has shown that no known enzyme system in the human can act on normal healthy cells. Thus our thinking was directed to a search for evidence to substantiate the vascular basis for hemorrhagic pancreatitis.

The various techniques listed in the literature were not effective in producing hemorrhagic pancreatitis in any large percentage of animals in our laboratories. In our own experience the following techniques failed:

1. injection of bile into the main pancreatic duct with or without ligation of the duct;

2. injection of trypsin or a combination of trypsin and bile into the main pancreatic duct, and

3. vagal stimulation following feeding of animals with or without ligation of both pancreatic ducts.

By the employment of a short, closed, duodenal loop obstruction, we were able to produce regularly acute hemorrhagic pancreatitis in dogs. This technique was employed because the duodenal loop and the head and body of the pancreas have a common blood supply, the superior pancreaticoduodenal artery. This method enabled us to check on the viability of the pancreatic tissue. Fortified with this technique, we undertook a study to determine sequential morphologic alterations in the course of the development of hemorrhagic pancreatitis. We were able to demonstrate by means of an hourly study, in which the several experimental animals were sacrificed at hourly

intervals, that by four hours, minute foci of extravasated red blood cells could be seen within scattered pancreatic acini. These lesions were definite and distinct by five hours and progressed rapidly until the 11 hour period, when involvement of both parenchyma and interstitial connective tissue was manifest. We used a more rigid histologic basis for hemorrhagic pancreatitis by separating the changes in the interstitial connective tissue from those in the parenchyma itself. For us, hemorrhagic pancreatitis is hemorrhage in the parenchyma, and not interstitial pancreatitis with hemorrhage.

Additional experiments were designed in order to find experimental evidence to support this vascular concept of hemorrhagic pancreatitis. The new evidence we have to substantiate our belief in the vascular basis as the common pathway is based on results obtained by the use of various-sized sterile polyethylene microspheres (8-400 microns), injected under controlled and comparable conditions into the superior pancreaticoduodenal artery, vein and pancreatic duct in 144 dogs. All animals were sacrificed at 72 hours except where the smallest microspheres (8-20 microns) were used. Here the animals were sacrificed at 11 hours to enable us to differentiate pathologic changes from autolysis. Pathologic alterations in the head, body and tail of the pancreas were graded according to the degree of edema, hemorrhage and necrosis found in both the interstitial connective tissue and in the pancreatic parenchyma proper. We adhered to our previously mentioned rigid histologic criteria. Our results showed that in all dogs that had their arterial tree injected with 8-20 micron microspheres, there was produced a characteristic acute hemorrhagic pancreatitis in 11 hours. When 200-400 micron microspheres were used, the final result was some moderate degree of interstitial pancreatitis in 72 hours.

The severity of the lesion was inversely proportional to the size of the microspheres; the larger the microsphere the less severe the lesion. The injection into the veins and pancreatic ducts of various-sized microspheres showed no significant changes when the animals were uniformly sacrificed at 72 hours. Minimal lesions occurred with the microspheres in the venous channels, and negligible changes when they were introduced into the duct system.

In summary, this work demonstrates the production in 11 hours of acute hemorrhagic pancreatitis by the injection of microspheres, 8-20 microns in diameter, into the pancreatico-duodenal artery in dogs; lesser degrees of pancreatitis occurred with larger microspheres. This additional evidence helps to substantiate the vascular basis of hemorrhagic pancreatitis as the common pathway which interferes with the pancreatic parenchymal viability, thus allowing the intrinsic enzyme systems to act on this altered parenchyma.

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DISCUSSION

DAVID A. DREILING: It is a privilege to discuss this interesting paper because my colleagues and I have been investigating the intriguing concepts developed by Dr. Safadi and his co-workers.

When the Pfeffer duodenal loop procedure was first reported at the Surgical Forums for Fundamental Research, the question was posed as to whether this mechanism was important in the pathogenesis of human pancreatitis, or whether it merely represented another artificial means of inciting pancreatitis by vascular stasis. Clinical observations during the past year have indicated that duodenal obstruction *is* an etiology of pancreatic inflammation *in man*. The first three slides will illustrate six cases in which chronic duodenal obstruction was associated with pancreatitis.

Convinced by these clinical findings that chronic duodenal obstruction does play a role in the pathogenesis of pancreatitis, Dr. Augusto Paulino Netto, the Ralph Colp

Surgical Fellow in my laboratory, undertook a study of the Pfeffer duodenal preparation. The pathologic sections were graciously done for us by Dr. Fenton Schaffner. The procedure of study was similar to that presented by Dr. Safadi, with the exception that the dogs were permitted to survive up to 48 hours.

The control group displayed much the same pathologic changes reported by Dr. Safadi. Although there is obviously some variation in the severity of the lesion, half of the animals died before 48 hours and presented fat necrosis, interstitial edema and abscess, hemorrhage, and abscess formation.

The administration of an anticholinergic (antisecretory) compound prior to and following the preparation of the duodenal loop did not alter the pathologic findings. The results were similar to those in the control animals.

When a Butazolidin metabolite prepared by Geigy was given to the dogs pre- and postoperatively, a marked interference with the development of lesions was noted. This is similar to the observations reported for propylthiouracil. We have no explanation at present for the mechanism by which Butazolidin protects against the development of hemorrhagic pancreatitis.

In order to determine whether duodenal obstruction, *per se*, contributed to the pathogenesis of this variety of pancreatitis, the Pfeffer procedure was modified by the introduction of a cannula into the main pancreatic duct at the time of duodenal ligation. The results of this manoeuver clearly demonstrated that when pancreatic ductal decompression was adequate, hemorrhagic pancreatitis did not develop. We have also noted that in those animals in which there was a perforation of the duodenal loop, death was delayed and the resulting pancreatitis was relatively mild. This complication occurred in six animals.

These findings have been interpreted as indicating that duodenal obstruction and the intrapancreatic ductal hypertension resulting from a pancreas secreting into a closed duodenal loop are important factors in the production of the pancreatitis in these animals.

Now let us consider the evidence presented for a vascular basis of pancreatitis. I think there are few investigators who will not concede an important place for the vascular factor in determining the extent and severity of the lesion in both human and experimental pancreatitis. As Popper and Necheles so beautifully demonstrated, arterial occlusion could convert pancreatic edema into pancreatic hemorrhagic necrosis. Arteriography in our animals is consistent with this concept that there is a diminution of arterial cross-sectional area in pancreatic edema and a marked reduction, almost to obliteration, in pancreatic necrosis. But is this change a primary one, or rather a result of edema within the parenchyma?

The physiologic question provoked by the presentation is whether there is convincing evidence for a primarily vascular etiology of pancreatitis. I think the evidence is suggestive but not convincing. First, I must ask whether the very early signs of parenchymal hemorrhage reported by Dr. Safadi may not be due to surgical trauma. It is impossible to prepare the Pfeffer animal without considerable operative manipulation of the pancreas. If this is not so, then one must assume the ligation of the duodenal wall produces an immediate vascular reaction. This can only be venous if the effect is mechanical. Yet Dr. Safadi has shown that injection of microspheres into the veins produced a minimal lesion. On the other hand, if the action of duodenal ligation was a reflex closure of the arterioles, the lack of protection afforded by the anticholinergic drug is rather disappointing.

Dr. Safadi's results with the injection of microspheres into the arteries are intriguing; but I do not believe they can be applied to the elucidation of the mechanism of pancreatitis in the Pfeffer dog. The devastating effect of small arteriolar occlusion by the smallest microspheres fits in more aptly with the auto-immune mechanism for pancreatic inflammation as propounded by Thal and others, but this is hypothesis whose proof or disproof lies with the pathologist and immunologist.

May I congratulate Dr. Safadi and his colleagues on their stimulating and original investigations?

H. M. ZIMMERMAN: May I interject just one comment, that perhaps it is time we begin to differentiate the lesions we see in the pancreas, other than tumors. The so-called hemorrhagic pancreatitides should be called by perhaps more precise anatomic terms, such as hemorrhagic infarction of the pancreas, or apoplexy of the pancreas, or something other than hemorrhagic pancreatitis. In many instances we see lesions which are pancreatitis all right, but are not hemorrhagic; and sometimes we see hemorrhage in the pancreas, but no evidence of inflammatory change. I believe Dr. Dreiling showed at least one slide which had both hemorrhage and inflammatory change. And some of the things he demonstrated and called abscesses, some of us would not call abscesses, but rather focal necrosis. It might be well, in a field where there has been so much controversy as to mechanism, to try to define the terms more precisely on an anatomic basis. This is by no means a criticism, because I myself am frequently guilty of talking about hemorrhagic pancreatitis when I really mean hemorrhage into the pancreas.

Now I would like to have Dr. Safadi answer the questions asked.

DAVID SAFADI: The only comment I would like to make is that in our particular experiments presented this evening, we did not have the Pfeffer duodenal loop in the dogs. The blood vessels were injected with microspheres, and a hemorrhagic pancreatitis was produced, thus verifying Dr. Pfeffer's method. In addition, the tail of the pancreas in the dog has an independent blood supply, and this acts as a check and balance. Since Dr. Dreiling, who is a surgeon, posed the question as to whether the pancreas can be approached without production of trauma, I would like to have this question, "if the pancreas can be prepared without traumatizing," answered by another surgeon. I would not like to be caught in the middle, that is, between one surgeon against another. I wonder if Dr. Pfeffer would like to comment on this phase.

ROBERT B. PFEFFER: Actually I agree with what Dr. Dreiling has done; it certainly possesses some aspects which are a little different from ours, and yet not so different. Dr. Dreiling pointed out that the vascular basis is important, and also that pancreatic ductal obstruction is important, and I am inclined to agree that pancreatic ductal obstruction may play some part in this vascular basis. We know that hyperplasia of the ductal epithelium may be significant, and in the closed duodenal loop I believe that ductal obstruction certainly can transmit increased pressure back to the acinus. If the acinus becomes edematous, the peripheral blood supply can be compressed. Our idea stems from work by Dr. L. Corsan Reid, who feels no enzyme system known can destroy a healthy living cell. I do not know what causes edematous or interstitial pancreatitis, but in hemorrhagic pancreatitis we feel it is the impairment of the blood supply to the individual cell which causes the breakdown of the cell. Perhaps pancreatic ductal obstruction is another factor which must be reckoned with, and I was glad to see the clever method Dr. Dreiling used in his experiments to demonstrate this factor.

H. M. ZIMMERMAN: Dr. Dreiling, it would not be becoming of us not to give you the opportunity to reply to these comments.

DAVID A. DREILING: I think you made one of the most pertinent remarks. At present we who are investigating the pancreas are in a state where the hepatologist was 20 years ago with regard to acute catarrhal jaundice. Essential for diagnosis is a thorough understanding of pathology; we cannot clarify our concepts of the pathogenesis until the pathologists give us the morphologic basis for accurate diagnosis. The second comment I would like to make is that we cannot glibly accept unproved premises. I think Dr. Pfeffer is perfectly right, and I would like to think that pancreatic edema results in an interference with blood supply to the pancreas and that the combination produces hemorrhagic pancreatitis. But let me point out that we have such a thing in man as mumps pancreatitis, in which there is pancreatic edema, but never hemorrhagic pancreatitis. These patients have swollen pancreases which are as edematous as can be, but no hemorrhagic pancreatitis.

Extrapancreatic Tumors Associated with Hypoglycemia

VIRGINIA KNEELAND FRANTZ

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A review of 25 cases of extrapancreatic tumors, presumably of mesodermal origin, was presented in table form. The term mesodermal was thought to be applicable not only to the tumors classified as fibrosarcoma, mesothelioma, etc., but also, on an embryological basis, to tumors arising in the adrenal cortex as well as those of possible ovarian origin. The table actually presented only contained 22 of the 25 cases, in order of publication. Three other cases which did not appear on the table were supplemented by comment. Two cases of extensive tumor associated with hypoglycemia, and often included in reports of extrapancreatic tumors, were excluded, although mentioned and bringing the total to 27. These were reported by Rosenfeld in 1949 and interpreted as pseudomyxoma peritonei, almost certainly of epithelial origin. Up to the end of 1957, 345 cases of *hyperinsulinism* due to islet cell tumors of the pancreas had been reported. This figure is to be contrasted with only 16 of these exceedingly rare tumors up to the same date. None of the tumors reported had any histologic resemblance to islet cell tumors. The symptoms were relieved by the removal of these tumors and in the case of those which were malignant, recurrences or metastases were associated with a return of symptoms in all but one case. The onset or recurrence of hypoglycemic symptoms was documented as occurring only when the tumor reached large size.

The breakdown of sites of origin was:

Abdominal cavity:

Adrenal	3
Retroperitoneal	3
Kidney	5
Pelvis	2
Ovary	1
Peritoneum—surface	3
Liver	3
Jejunum	1

Thorax:

Mediastinum	1
Diaphragm	3

The authors' diagnoses were*:

Carcinoma of adrenal cortex	3
Sarcomatous dysembryoplasia with corticoadrenal differentiation	1
Fibroma	2
Fibrosarcoma	5
Spindle cell sarcoma	4
1 without qualification	
1 with ? Beta granules	
2 with metastases	
Hemangiopericytoma	1
Liposarcoma	1
Leiomyosarcoma	1
Malignant mesothelioma	2
Malignant mesodermal tumor, type ?	1
Fibrous mesothelioma	3
2 without qualification	
1 resembling thecoma	
Sarcoma, type ?, involving ovary (? granulosa cell tumor)	1

It should be noted that except for the tumors associated with the adrenal and possibly with the ovary and the mesotheliomas, all of these diagnoses are consistent with huge tumors of soft parts outside the abdomen and thorax, the largest being usually in the thigh or buttocks. Yet none of these tumors, similar histologically, outside of the serous cavities, have been associated with hypoglycemia.

The sexes were 15 men and 10 women. Three of the latter were teen-age girls with tumors associated with the adrenal, two with reported masculinization. The one male with an adrenal cortical tumor and feminization was 25. The preponderance of males was in the fifth and sixth decades. Most of the tumors were retroperitoneal and most of them very large, from "grape-

* Skillern modified—later personal communication, Dr. Crile.

fruit" to "football" in size. Insulin assay was attempted in nine and was positive in only two, both thoracic fibrous tumors arising from the diaphragm.

No conclusion was reached except a suggestion relative to the "totipotentiality of the mesenchyme". The cases presented in detail were from the authors Scholtz, Woolner and Priestley; Howard, J. W. and Davis, P. L.; McLeod, C.; and Porter and Frantz.

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DISCUSSION

BRUNO W. VOLK: I should like to add another case to the list of Dr. Frantz. The patient was a 69 year old man who had a rapidly growing abdominal tumor, and, if I remember correctly, had repeated episodes of hypoglycemia with blood sugar levels dropping as low as 10 mg. per 100 ml. during the last three months of life.

At autopsy the tumor weighed 8,000 grams and was confined to the root of the mesentery. Histologically it was a fibrosarcoma. Dr. Renold of Boston, who was kind enough to perform an assay for insulin-like substances, obtained what would amount to 20 units of insulin for the entire neoplasm. This would only equal the insulin content of a normal adult pancreas. The question arises as to the cause of hypoglycemia in these cases.

Dr. Frantz demonstrated the pathology of these tumors most beautifully. I should like to ask whether she has some explanation for the hypoglycemia occurring in these instances in extrapancreatic tumors.

MARTIN G. GOLDNER: I am pleased that Dr. Volk mentioned this case of ours, but I believe that he was too modest. He could have mentioned three instances of severe hypoglycemia in extra-pancreatic malignancies which we observed in recent months at the Jewish Chronic Disease Hospital in Brooklyn. The two other tumors were not sarcomata, but carcinomata, a fact which seems to complicate the situation even further. Both patients had metastatic disease; one had a carcinoma of the stomach, the other a bronchogenic carcinoma with a history of diabetes. Both came to autopsy. No significant endocrine involvement was found, and the livers, although

full of metastases, were not devoid of glycogen. Both patients had marked hypoglycemia during the last month of life. Assays for insulin-like activity in the blood of these two patients were obtained through the kind cooperation of Dr. Renold, of Boston, who uses the method of glucose uptake of the epididymal fat pad of the rat[1]. The assay was negative for the case of bronchogenic carcinoma, but a marked, increased insulin-like activity was found in the blood of the patient with gastric carcinoma. In the same case a high plasma insulin concentration was demonstrated by Yalow and Berson with their immunochemical method[2]. It seems, therefore, that the hypoglycemia in this case can be ascribed to increased insulin or insulin-like material in the blood and may not be due to cachexia or emaciation, where low blood sugar levels are found not infrequently.

With regard to the mechanism of the hypoglycemia in such cases, I wonder whether Dr. Frantz is familiar with the case of Sellman and associates[3]. This group analyzed the amino acid content of the tumor and found an unusually high concentration of various amino acids, with the highest concentration of leucine. Since leucine is known to cause hypoglycemia in sensitive individuals, one may speculate, as Stern[4] has already done, that this amino acid may be related to this phenomenon in extrapancreatic tumors.

ABRAHAM KANTROWITZ: Recently a patient had an open thoracotomy and a posterior mediastinal tumor was removed. The pathologic diagnosis was neuroblastoma, posterior mediastinum. The patient had had several bouts of hypoglycemia with blood sugar running as low as 10 mg. per 100 ml. The patient was 19 years of age. The tumor measured 6 cm. at its greatest diameter. The ribs, as well as the apex of the left lung, were invaded. The patient's symptoms seemed to be ameliorated, but within a few months she returned with evidence of skull metastases in two separate areas. Her hypoglycemic attacks seemed to become worse. The patient was lost to another hospital.

VIRGINA KNEELAND FRANTZ: I see by the program I have an out. There is an executive session, and I know the rule of this society is that we have to get out of this room very promptly.

As you all are aware, I was never certified in pathologic anatomy. I got in because of old age. Nor have I been certified in clinical pathology. In answer to Dr. Goldner, I have heard of leucine and amino acids, but I am not really qualified to speak on this subject. I think I have the Sellman case he mentioned at the tail end of the table, but it is not on the lantern slide. I hope that Dr. Volk will put his case in print. All the cases I have reported, from the earliest ones, have been published. I found in my struggles to get the numbers correct that cases were apt to be published over and over again, particularly those listed as personal communications. I have tried to avoid quoting cases, therefore, that are not in print. Yet I would love to have another case. Dr. Volk, where has this been, or will this be, published?

BRUNO W. VOLK: It is in press in *Geriatrics* as a C.P.C.

VIRGINIA KNEELAND FRANTZ: I can avoid discussing the tumor of the lung and the tumor of the stomach by saying that my cases were limited to tumors of mesodermal origin, although I alluded to Rosenfeld's two cases of pseudomyxoma peritonei. Dr. Goldner's carcinoma cases are obviously cases of advanced disease. I would hesitate to accept in this particular group, without careful scrutiny, any case in which it was not shown that the removal of the tumor alleviated the symptoms, and that these did not return until recurrence of the tumor.

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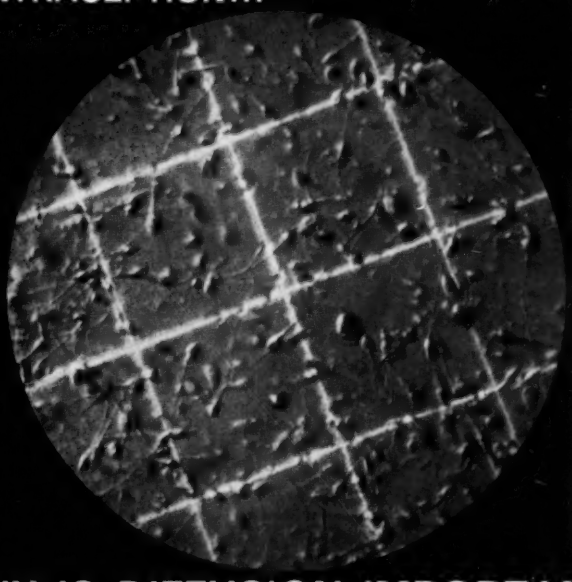

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